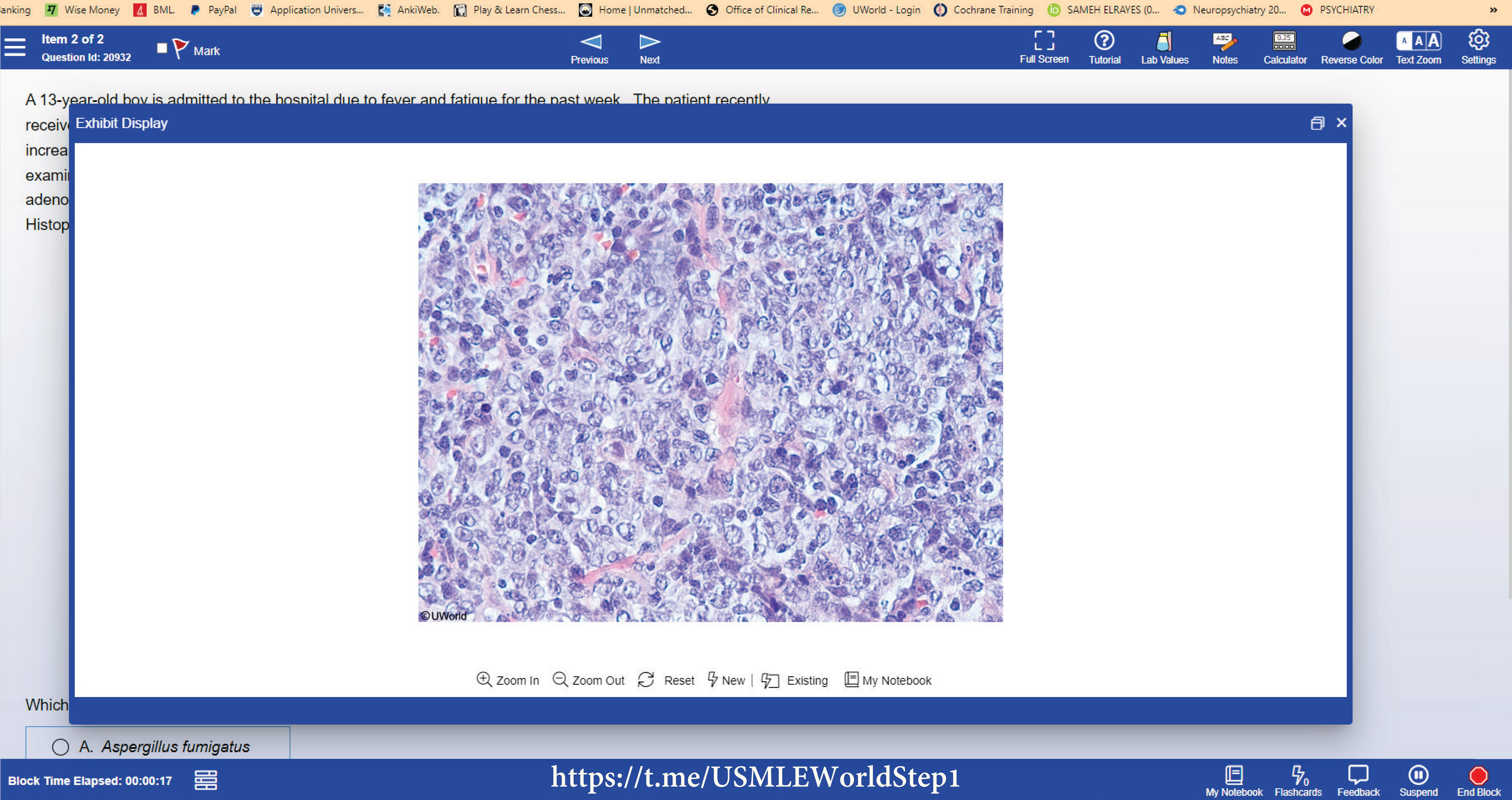

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 2 of 2
Question Id: 20932

A 13-year-old boy is admitted to the hospital due to fever and fatigue for the past week. The patient recently

receiv

increa

exami

adeno

Histop

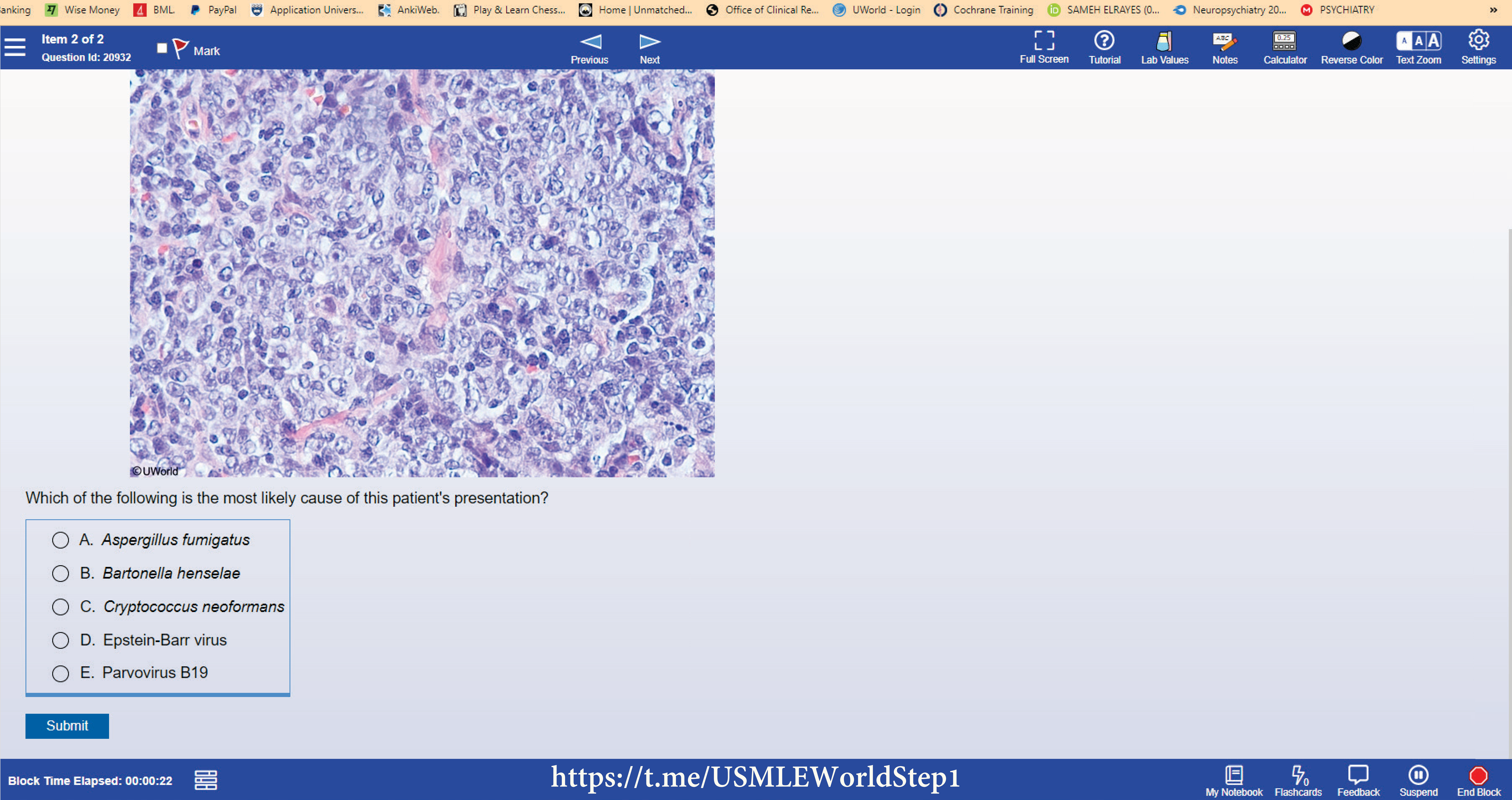
Exhibit Display

©UWorld

Which

○ A. *Aspergillus fumigatus*

Block Time Elapsed: 00:00:17


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 2
Question Id: 20932
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Submit
Block Time Elapsed: 00:00:22
My Notebook
Flashcards
Feedback
Suspend
End Block

Which of the following is the most likely cause of this patient's presentation?

○ A. *Aspergillus fumigatus*

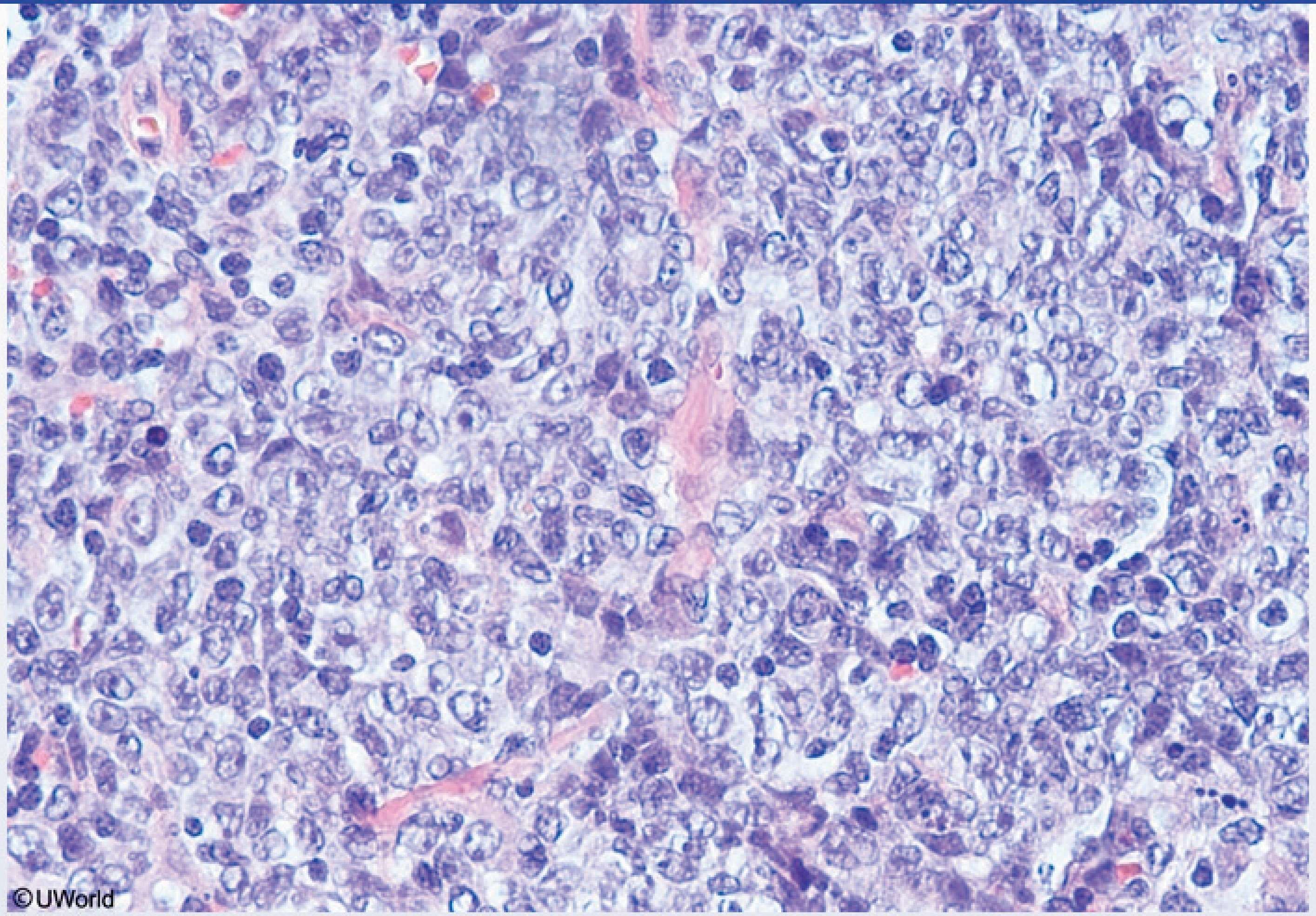
○ B. *Bartonella henselae*

○ C. *Cryptococcus neoformans*

○ D. Epstein-Barr virus

○ E. Parvovirus B19

https://t.me/USMLEWorldStep1



Which of the following is the most likely cause of this patient's presentation?

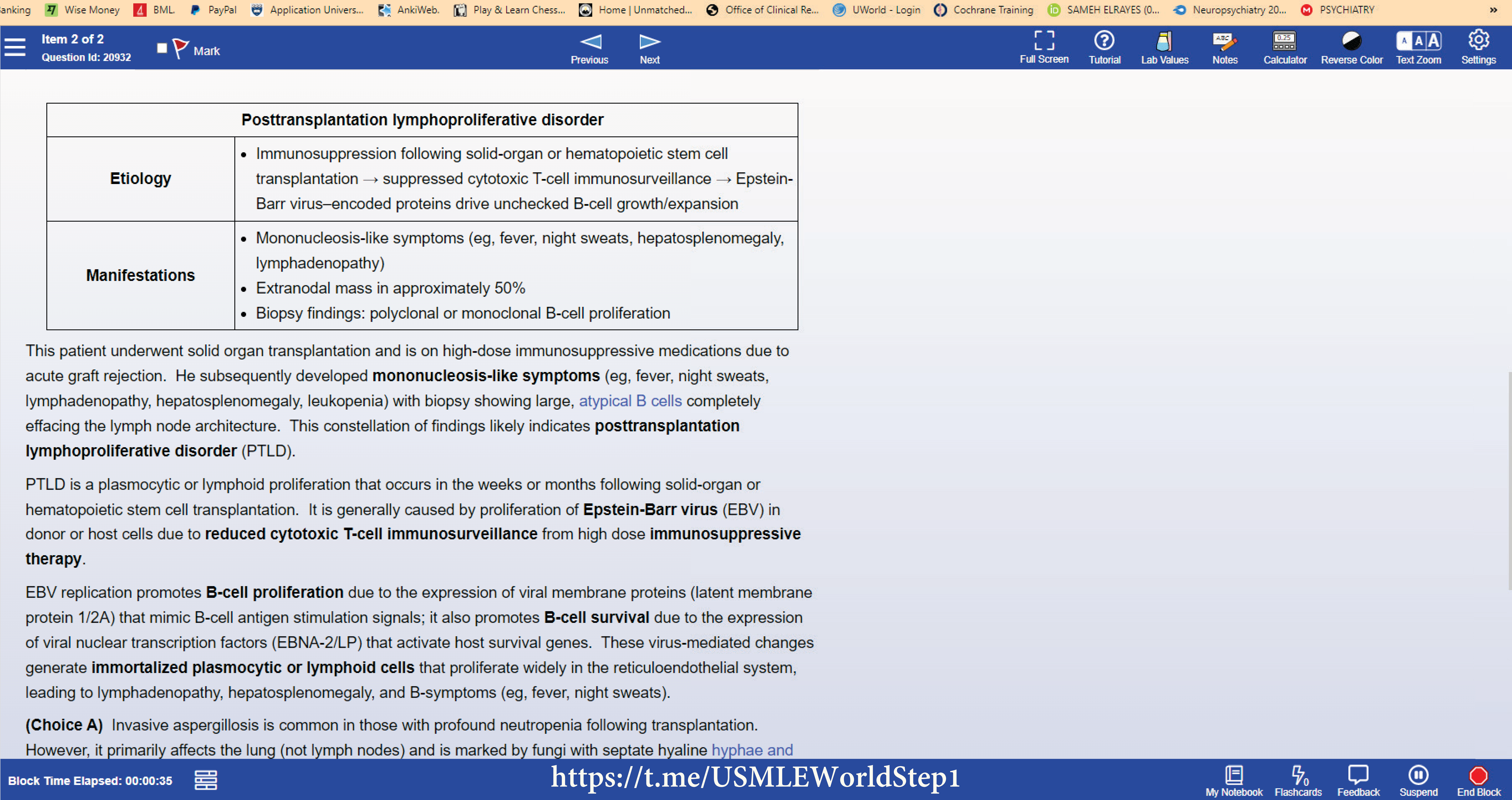
- ○ A. *Aspergillus fumigatus* (5%)
- ○ B. *Bartonella henselae* (12%)
- ○ C. *Cryptococcus neoformans* (3%)
- ✓ ● D. Epstein-Barr virus (70%)
- ○ E. Parvovirus B19 (7%)

Correct

70%
Answered correctly

25 secs
Time Spent

2023
Version


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 2
Question Id: 20932
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Posttransplantation lymphoproliferative disorder	
Etiology	• Immunosuppression following solid-organ or hematopoietic stem cell transplantation → suppressed cytotoxic T-cell immunosurveillance → Epstein-Barr virus–encoded proteins drive unchecked B-cell growth/expansion
Manifestations	• Mononucleosis-like symptoms (eg, fever, night sweats, hepatosplenomegaly, lymphadenopathy) • Extranodal mass in approximately 50% • Biopsy findings: polyclonal or monoclonal B-cell proliferation

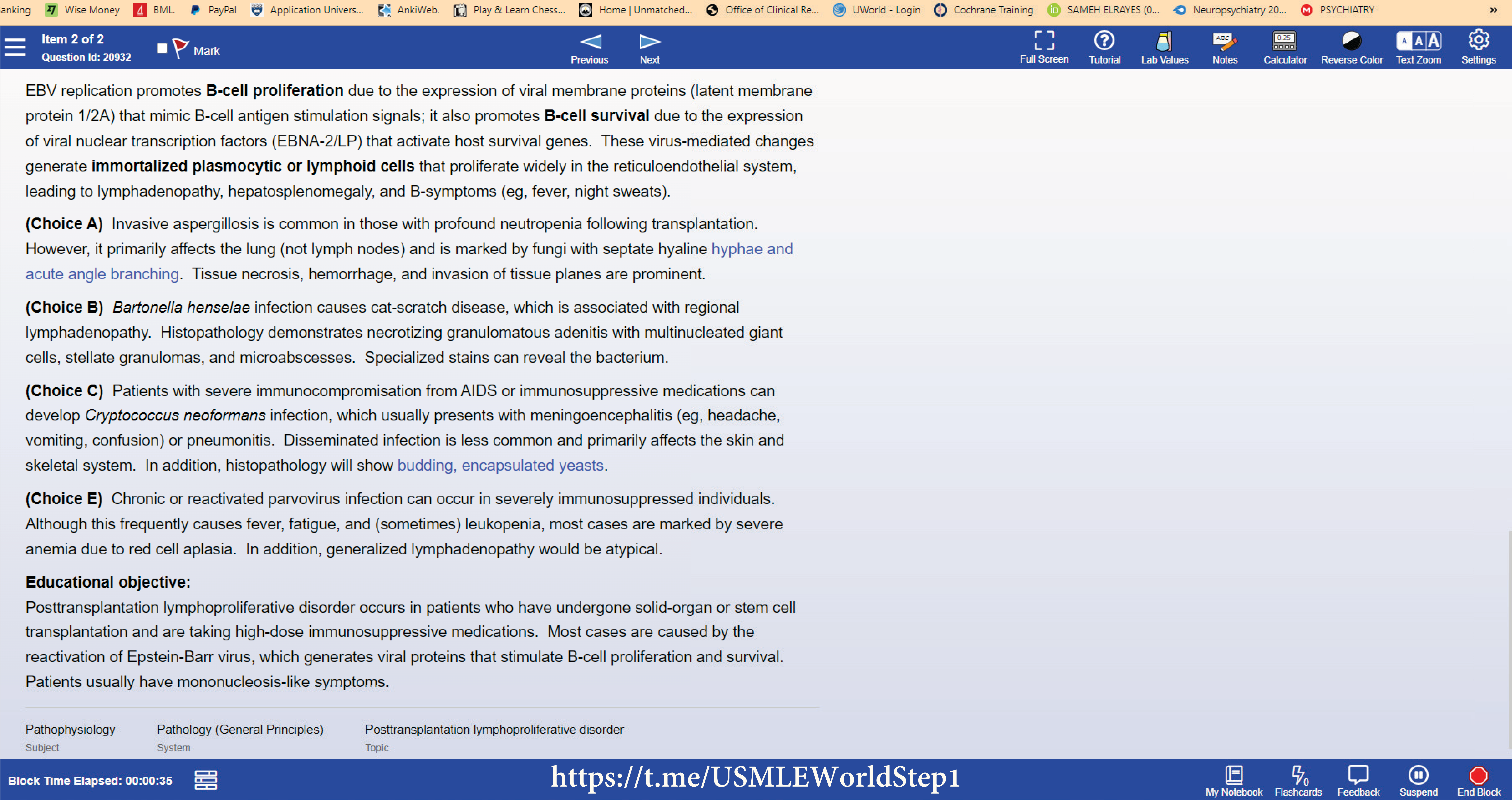
This patient underwent solid organ transplantation and is on high-dose immunosuppressive medications due to acute graft rejection. He subsequently developed **mononucleosis-like symptoms** (eg, fever, night sweats, lymphadenopathy, hepatosplenomegaly, leukopenia) with biopsy showing large, atypical B cells completely effacing the lymph node architecture. This constellation of findings likely indicates **posttransplantation lymphoproliferative disorder** (PTLD).

PTLD is a plasmocytic or lymphoid proliferation that occurs in the weeks or months following solid-organ or hematopoietic stem cell transplantation. It is generally caused by proliferation of **Epstein-Barr virus** (EBV) in donor or host cells due to **reduced cytotoxic T-cell immunosurveillance** from high dose **immunosuppressive therapy**.

EBV replication promotes **B-cell proliferation** due to the expression of viral membrane proteins (latent membrane protein 1/2A) that mimic B-cell antigen stimulation signals; it also promotes **B-cell survival** due to the expression of viral nuclear transcription factors (EBNA-2/LP) that activate host survival genes. These virus-mediated changes generate **immortalized plasmocytic or lymphoid cells** that proliferate widely in the reticuloendothelial system, leading to lymphadenopathy, hepatosplenomegaly, and B-symptoms (eg, fever, night sweats).

(Choice A) Invasive aspergillosis is common in those with profound neutropenia following transplantation. However, it primarily affects the lung (not lymph nodes) and is marked by fungi with septate hyaline hyphae and

Block Time Elapsed: 00:00:35
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 2
Question Id: 20932
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

EBV replication promotes **B-cell proliferation** due to the expression of viral membrane proteins (latent membrane protein 1/2A) that mimic B-cell antigen stimulation signals; it also promotes **B-cell survival** due to the expression of viral nuclear transcription factors (EBNA-2/LP) that activate host survival genes. These virus-mediated changes generate **immortalized plasmocytic or lymphoid cells** that proliferate widely in the reticuloendothelial system, leading to lymphadenopathy, hepatosplenomegaly, and B-symptoms (eg, fever, night sweats).

(Choice A) Invasive aspergillosis is common in those with profound neutropenia following transplantation. However, it primarily affects the lung (not lymph nodes) and is marked by fungi with septate hyaline hyphae and acute angle branching. Tissue necrosis, hemorrhage, and invasion of tissue planes are prominent.

(Choice B) *Bartonella henselae* infection causes cat-scratch disease, which is associated with regional lymphadenopathy. Histopathology demonstrates necrotizing granulomatous adenitis with multinucleated giant cells, stellate granulomas, and microabscesses. Specialized stains can reveal the bacterium.

(Choice C) Patients with severe immunocompromisation from AIDS or immunosuppressive medications can develop *Cryptococcus neoformans* infection, which usually presents with meningoencephalitis (eg, headache, vomiting, confusion) or pneumonitis. Disseminated infection is less common and primarily affects the skin and skeletal system. In addition, histopathology will show budding, encapsulated yeasts.

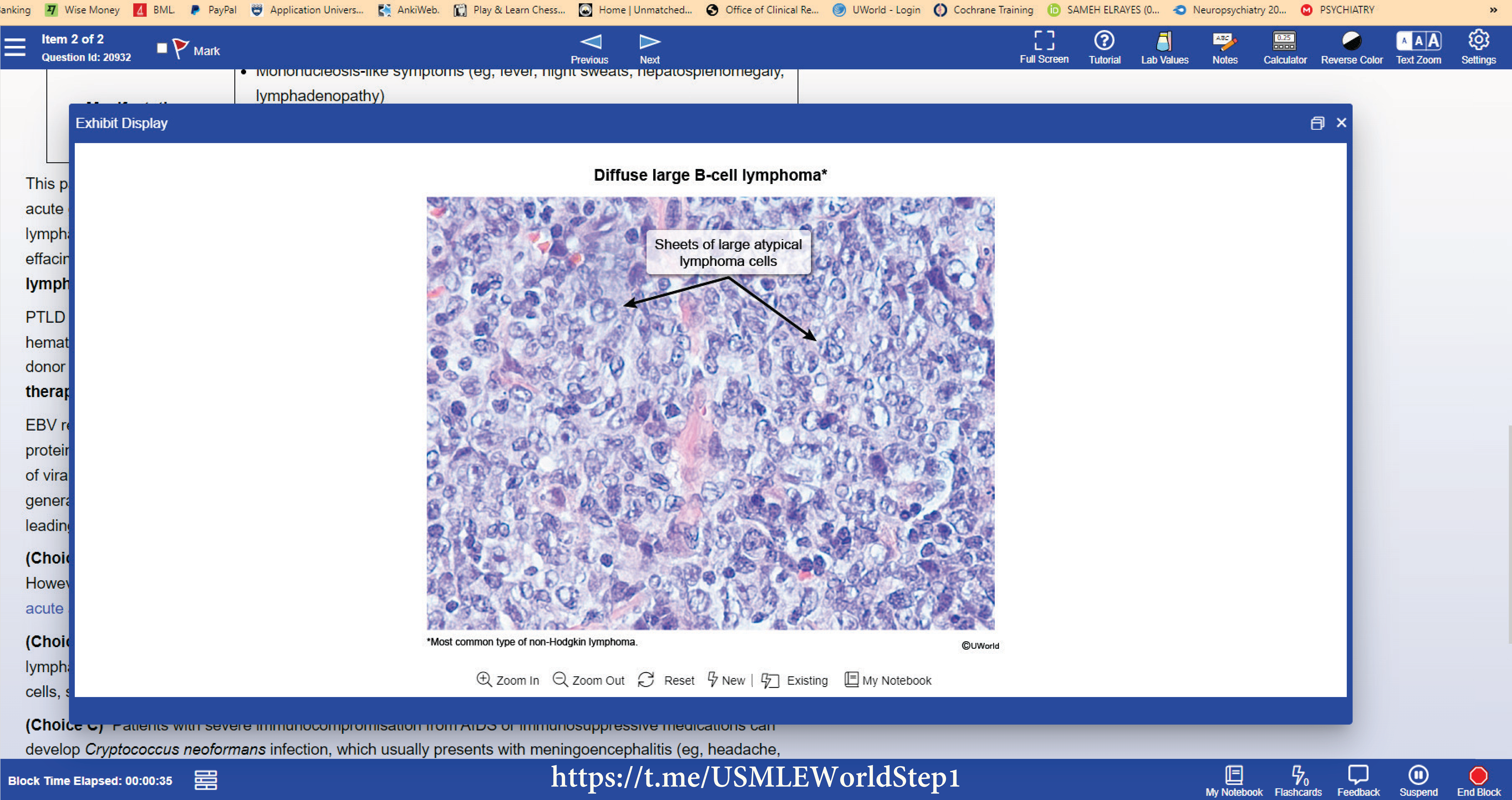
(Choice E) Chronic or reactivated parvovirus infection can occur in severely immunosuppressed individuals. Although this frequently causes fever, fatigue, and (sometimes) leukopenia, most cases are marked by severe anemia due to red cell aplasia. In addition, generalized lymphadenopathy would be atypical.

Educational objective:

Posttransplantation lymphoproliferative disorder occurs in patients who have undergone solid-organ or stem cell transplantation and are taking high-dose immunosuppressive medications. Most cases are caused by the reactivation of Epstein-Barr virus, which generates viral proteins that stimulate B-cell proliferation and survival. Patients usually have mononucleosis-like symptoms.

Pathophysiology	Pathology (General Principles)	Posttransplantation lymphoproliferative disorder
Subject	System	Topic

Block Time Elapsed: 00:00:35
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Sheets of large atypical lymphoma cells
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 2 of 2
Question Id: 20932

- Mononucleosis-like symptoms (eg, fever, night sweats, hepatosplenomegaly, lymphadenopathy)

This p
acute
lympha
effacin
lymph

PTLD
hemat
donor
therap

EBV r
protein
of vira
genera
leadin

(Choic
Howev
acute

(Choic
lympha
cells, s

(Choice C) Patients with severe immunocompromisation from AIDS or immunosuppressive medications can develop *Cryptococcus neoformans* infection, which usually presents with meningoencephalitis (eg, headache,

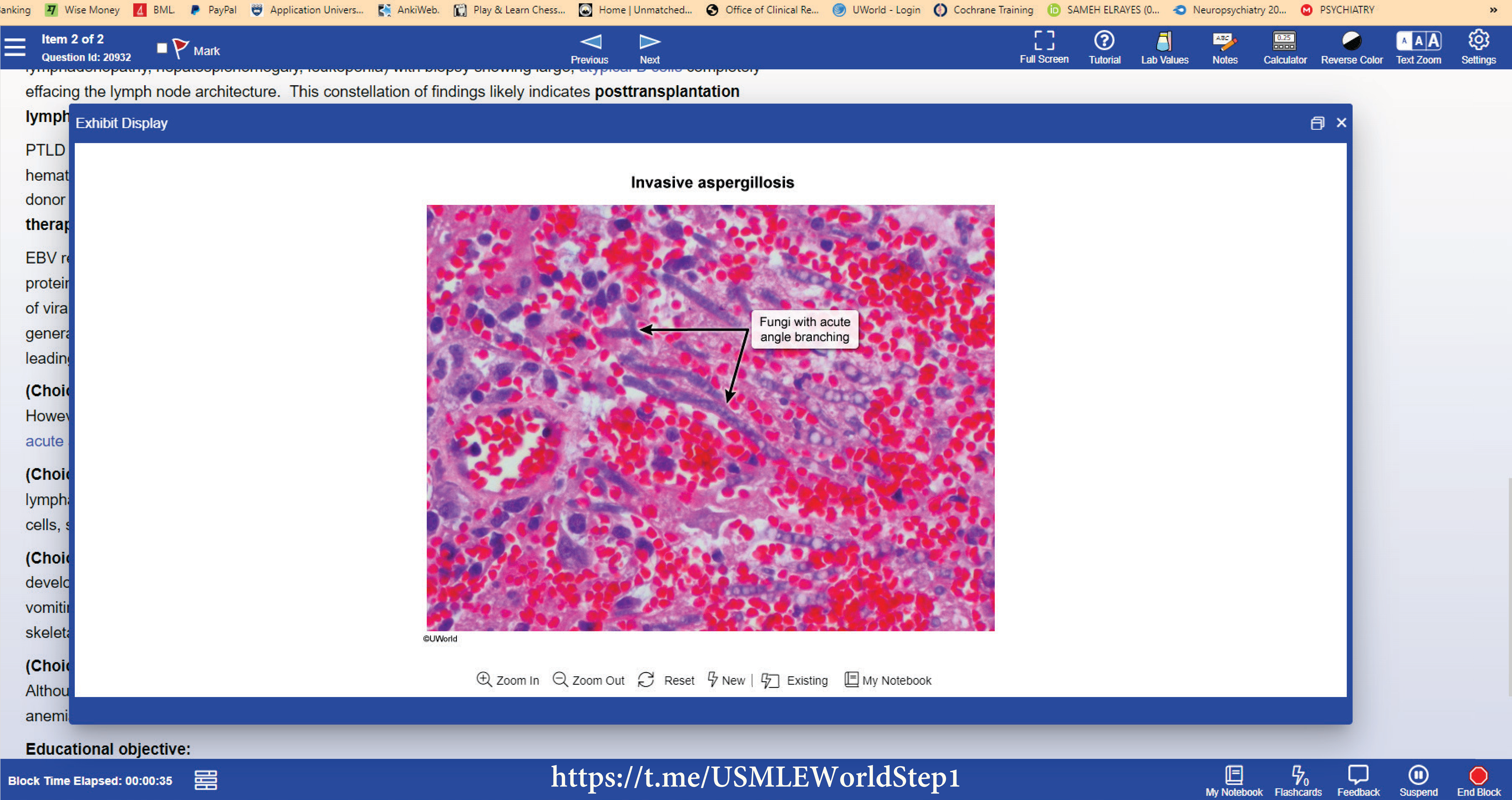
Exhibit Display

Diffuse large B-cell lymphoma*

*Most common type of non-Hodgkin lymphoma.

©UWorld

Block Time Elapsed: 00:00:35


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 2
Question Id: 20932
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

effacing the lymph node architecture. This constellation of findings likely indicates **posttransplantation**

lymph

PTLD

hemat

donor

therap

EBV r

protei

of vira

genera

leadin

(Choi

Howe

acute

(Choi

lymph

cells, s

(Choi

develo

vomiti

skelet

(Choi

Althou

anemi

Educational objective:

Exhibit Display

Invasive aspergillosis

Fungi with acute angle branching

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:00:35

My Notebook
Flashcards
Feedback
Suspend
End Block

protein 1/2A) that mimic B-cell antigen stimulation signals; it also promotes **B-cell survival** due to the expression

of vira

genera

leadin

(Choic

Howev

acute

(Choic

lymph

cells, s

(Choic

develo

vomiti

skelet

(Choic

Althou

anemi

Educa

Posttr

transp

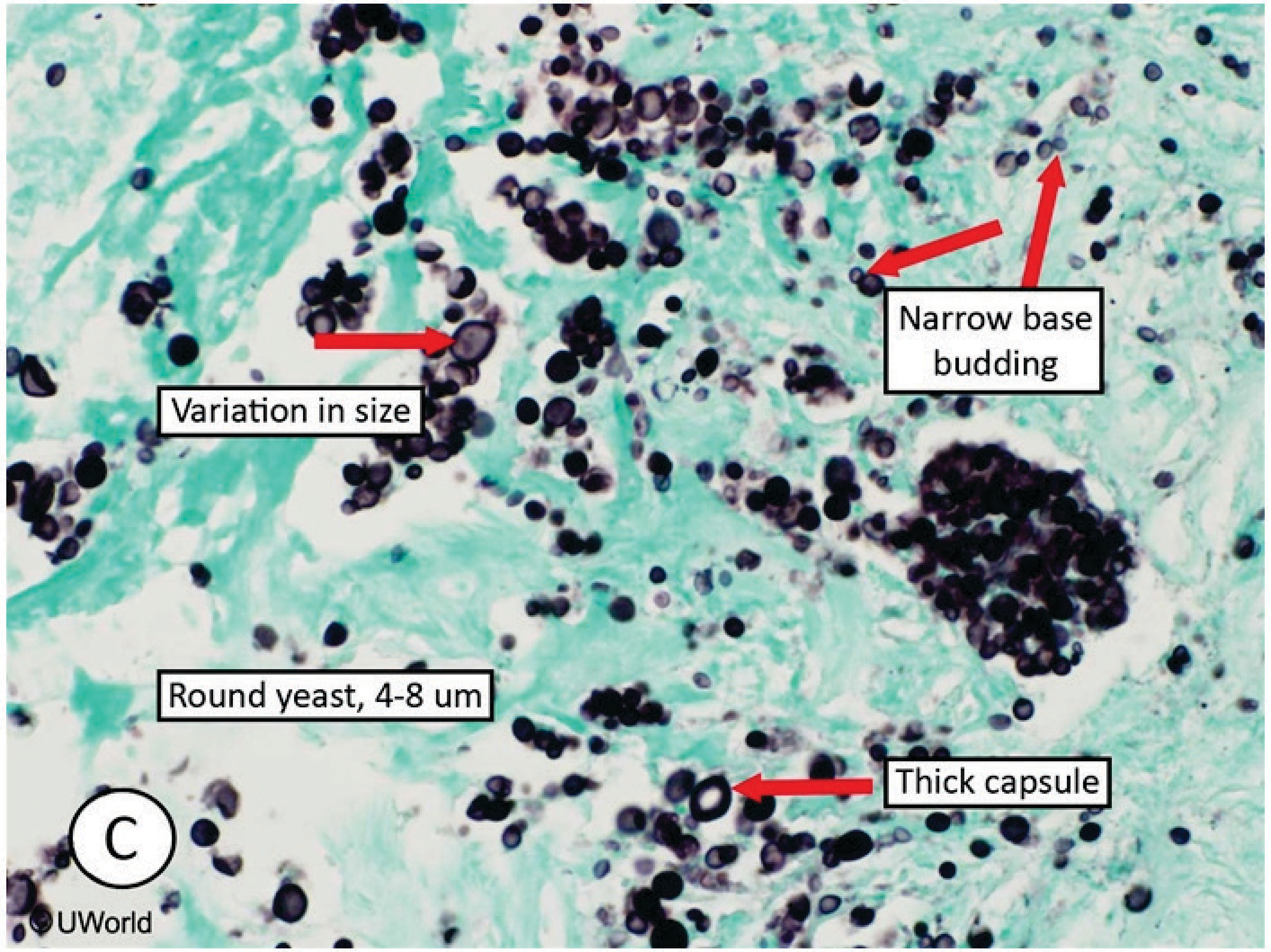
reactiv

Patien

Pathoph

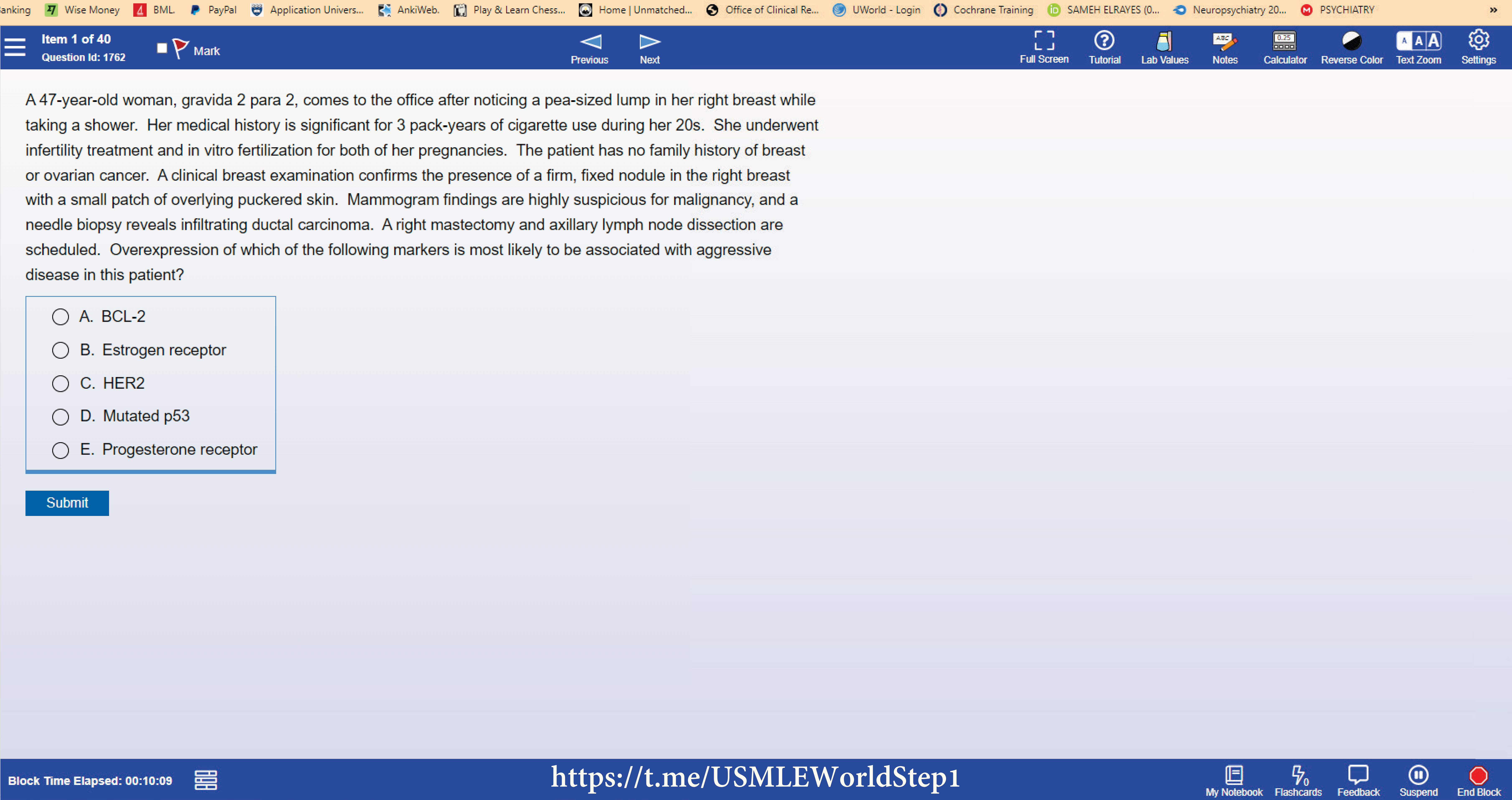
Subject

Exhibit Display



Zoom In Zoom Out Reset New | Existing My Notebook

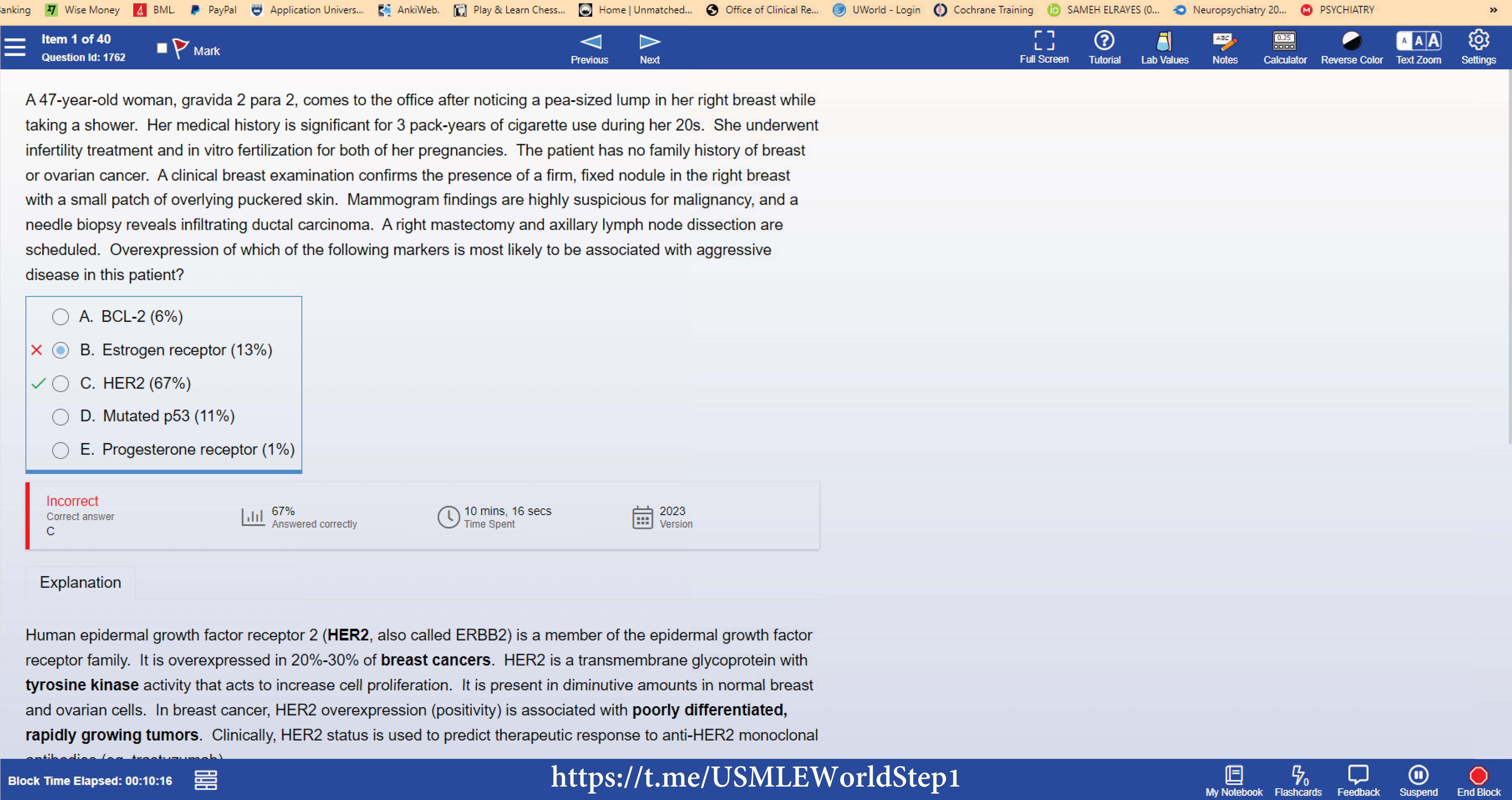
Copyright © UWorld. All rights reserved.


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 1 of 40
Question Id: 1762
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:10:09
My Notebook
Flashcards
Feedback
Suspend
End Block

A 47-year-old woman, gravida 2 para 2, comes to the office after noticing a pea-sized lump in her right breast while taking a shower. Her medical history is significant for 3 pack-years of cigarette use during her 20s. She underwent infertility treatment and in vitro fertilization for both of her pregnancies. The patient has no family history of breast or ovarian cancer. A clinical breast examination confirms the presence of a firm, fixed nodule in the right breast with a small patch of overlying puckered skin. Mammogram findings are highly suspicious for malignancy, and a needle biopsy reveals infiltrating ductal carcinoma. A right mastectomy and axillary lymph node dissection are scheduled. Overexpression of which of the following markers is most likely to be associated with aggressive disease in this patient?

○ A. BCL-2
○ B. Estrogen receptor
○ C. HER2
○ D. Mutated p53
○ E. Progesterone receptor

Submit


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 1 of 40
Question Id: 1762
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 47-year-old woman, gravida 2 para 2, comes to the office after noticing a pea-sized lump in her right breast while taking a shower. Her medical history is significant for 3 pack-years of cigarette use during her 20s. She underwent infertility treatment and in vitro fertilization for both of her pregnancies. The patient has no family history of breast or ovarian cancer. A clinical breast examination confirms the presence of a firm, fixed nodule in the right breast with a small patch of overlying puckered skin. Mammogram findings are highly suspicious for malignancy, and a needle biopsy reveals infiltrating ductal carcinoma. A right mastectomy and axillary lymph node dissection are scheduled. Overexpression of which of the following markers is most likely to be associated with aggressive disease in this patient?

- ○ A. BCL-2 (6%)
- ✗ ● B. Estrogen receptor (13%)
- ✓ ○ C. HER2 (67%)
- ○ D. Mutated p53 (11%)
- ○ E. Progesterone receptor (1%)

Incorrect
Correct answer
C

67%
Answered correctly

10 mins, 16 secs
Time Spent

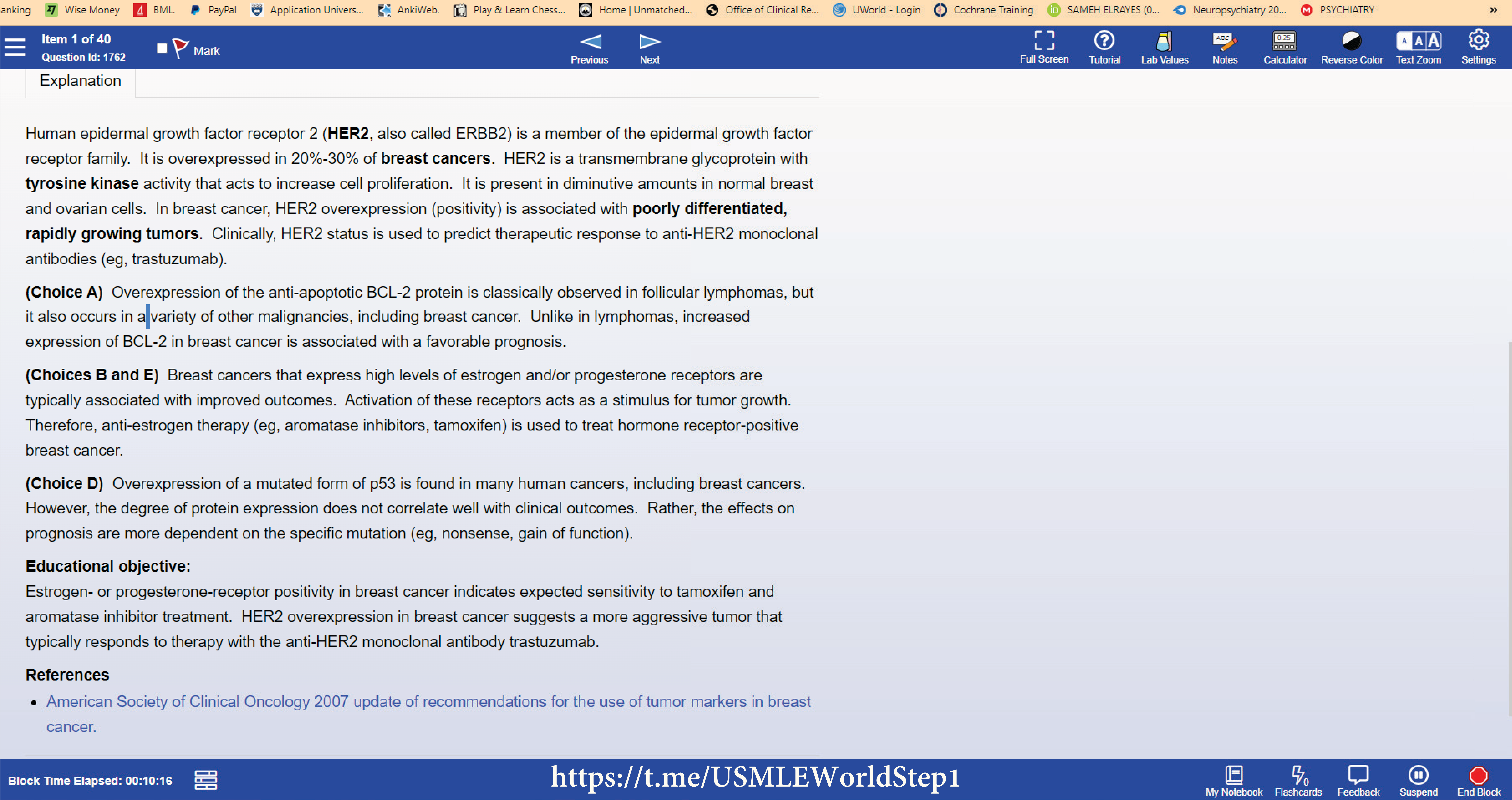
2023
Version

Explanation

Human epidermal growth factor receptor 2 (**HER2**, also called ERBB2) is a member of the epidermal growth factor receptor family. It is overexpressed in 20%-30% of **breast cancers**. HER2 is a transmembrane glycoprotein with **tyrosine kinase** activity that acts to increase cell proliferation. It is present in diminutive amounts in normal breast and ovarian cells. In breast cancer, HER2 overexpression (positivity) is associated with **poorly differentiated, rapidly growing tumors**. Clinically, HER2 status is used to predict therapeutic response to anti-HER2 monoclonal antibodies (eg, trastuzumab).

Block Time Elapsed: 00:10:16

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 1 of 40
Question Id: 1762
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Human epidermal growth factor receptor 2 (**HER2**, also called ERBB2) is a member of the epidermal growth factor receptor family. It is overexpressed in 20%-30% of **breast cancers**. HER2 is a transmembrane glycoprotein with **tyrosine kinase** activity that acts to increase cell proliferation. It is present in diminutive amounts in normal breast and ovarian cells. In breast cancer, HER2 overexpression (positivity) is associated with **poorly differentiated, rapidly growing tumors**. Clinically, HER2 status is used to predict therapeutic response to anti-HER2 monoclonal antibodies (eg, trastuzumab).

(Choice A) Overexpression of the anti-apoptotic BCL-2 protein is classically observed in follicular lymphomas, but it also occurs in a variety of other malignancies, including breast cancer. Unlike in lymphomas, increased expression of BCL-2 in breast cancer is associated with a favorable prognosis.

(Choices B and E) Breast cancers that express high levels of estrogen and/or progesterone receptors are typically associated with improved outcomes. Activation of these receptors acts as a stimulus for tumor growth. Therefore, anti-estrogen therapy (eg, aromatase inhibitors, tamoxifen) is used to treat hormone receptor-positive breast cancer.

(Choice D) Overexpression of a mutated form of p53 is found in many human cancers, including breast cancers. However, the degree of protein expression does not correlate well with clinical outcomes. Rather, the effects on prognosis are more dependent on the specific mutation (eg, nonsense, gain of function).

Educational objective:

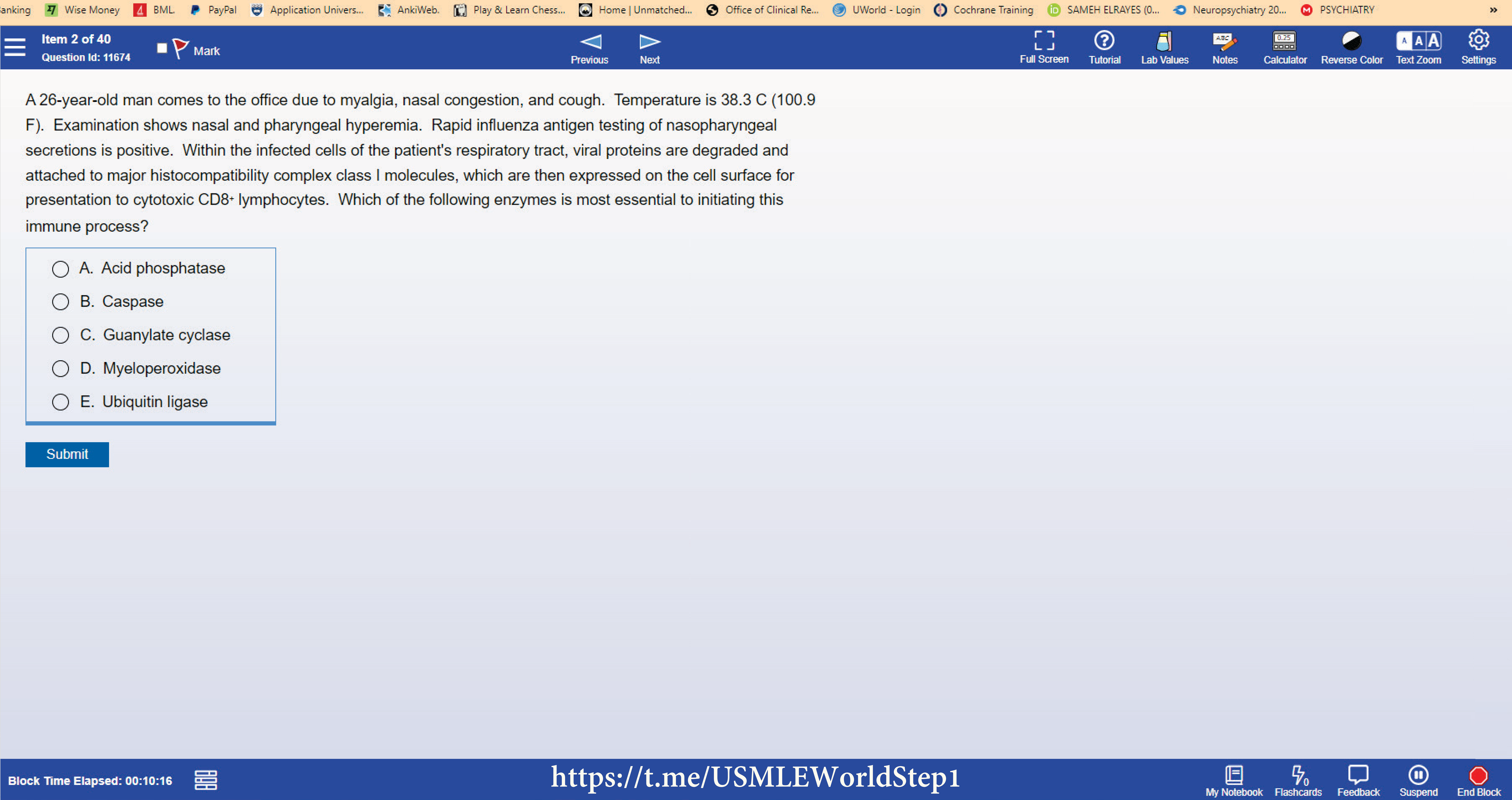
Estrogen- or progesterone-receptor positivity in breast cancer indicates expected sensitivity to tamoxifen and aromatase inhibitor treatment. HER2 overexpression in breast cancer suggests a more aggressive tumor that typically responds to therapy with the anti-HER2 monoclonal antibody trastuzumab.

References

- American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer.

Block Time Elapsed: 00:10:16

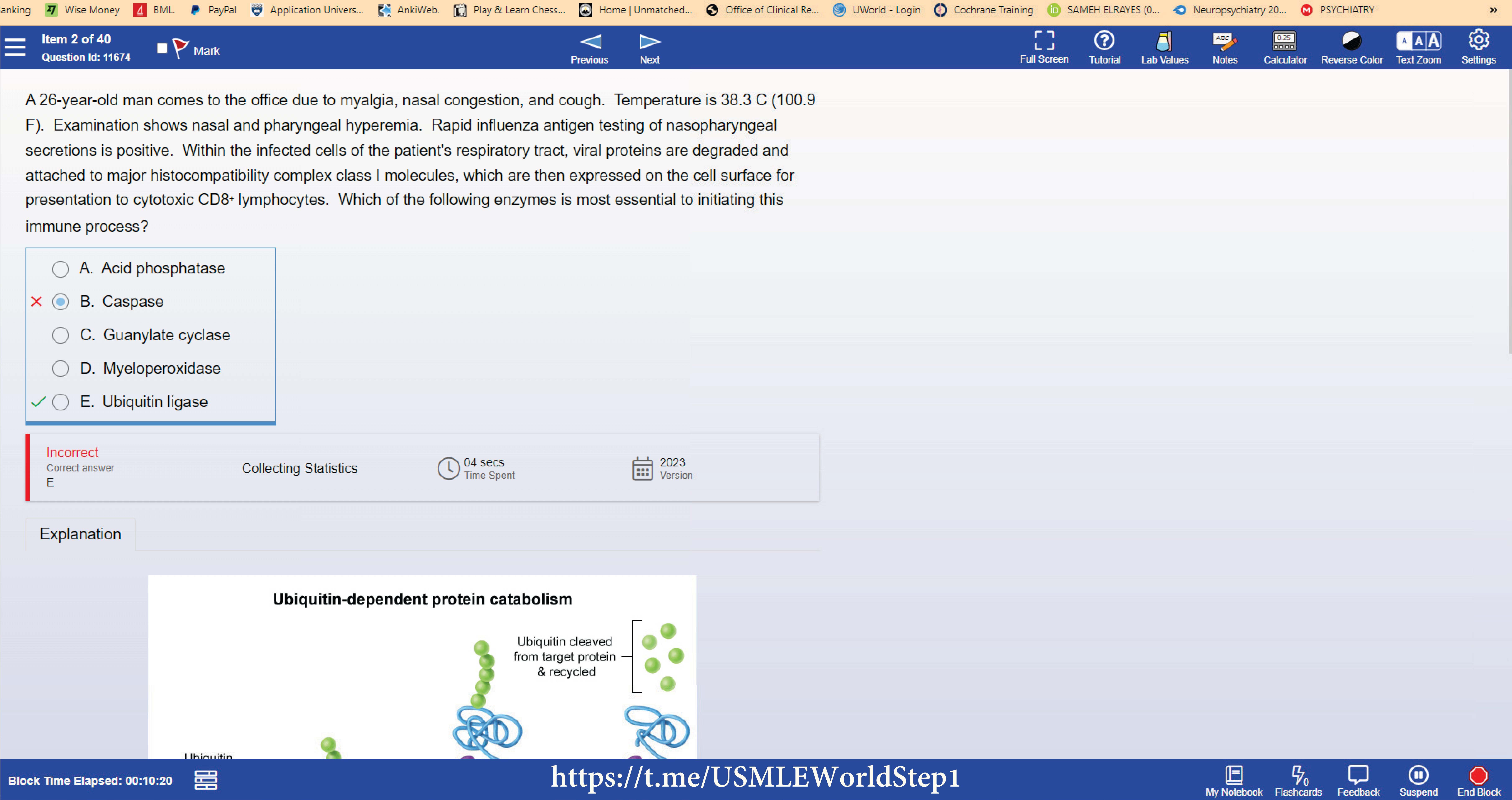
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 40
Question Id: 11674
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9 F). Examination shows nasal and pharyngeal hyperemia. Rapid influenza antigen testing of nasopharyngeal secretions is positive. Within the infected cells of the patient's respiratory tract, viral proteins are degraded and attached to major histocompatibility complex class I molecules, which are then expressed on the cell surface for presentation to cytotoxic CD8$^+$ lymphocytes. Which of the following enzymes is most essential to initiating this immune process?

○ A. Acid phosphatase
○ B. Caspase
○ C. Guanylate cyclase
○ D. Myeloperoxidase
○ E. Ubiquitin ligase

Submit
Block Time Elapsed: 00:10:16
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 40
Question Id: 11674
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9 F). Examination shows nasal and pharyngeal hyperemia. Rapid influenza antigen testing of nasopharyngeal secretions is positive. Within the infected cells of the patient's respiratory tract, viral proteins are degraded and attached to major histocompatibility complex class I molecules, which are then expressed on the cell surface for presentation to cytotoxic $CD8^+$ lymphocytes. Which of the following enzymes is most essential to initiating this immune process?

○ A. Acid phosphatase

✗ ● B. Caspase

○ C. Guanylate cyclase

○ D. Myeloperoxidase

✓ ○ E. Ubiquitin ligase

Incorrect
Correct answer
E

Collecting Statistics

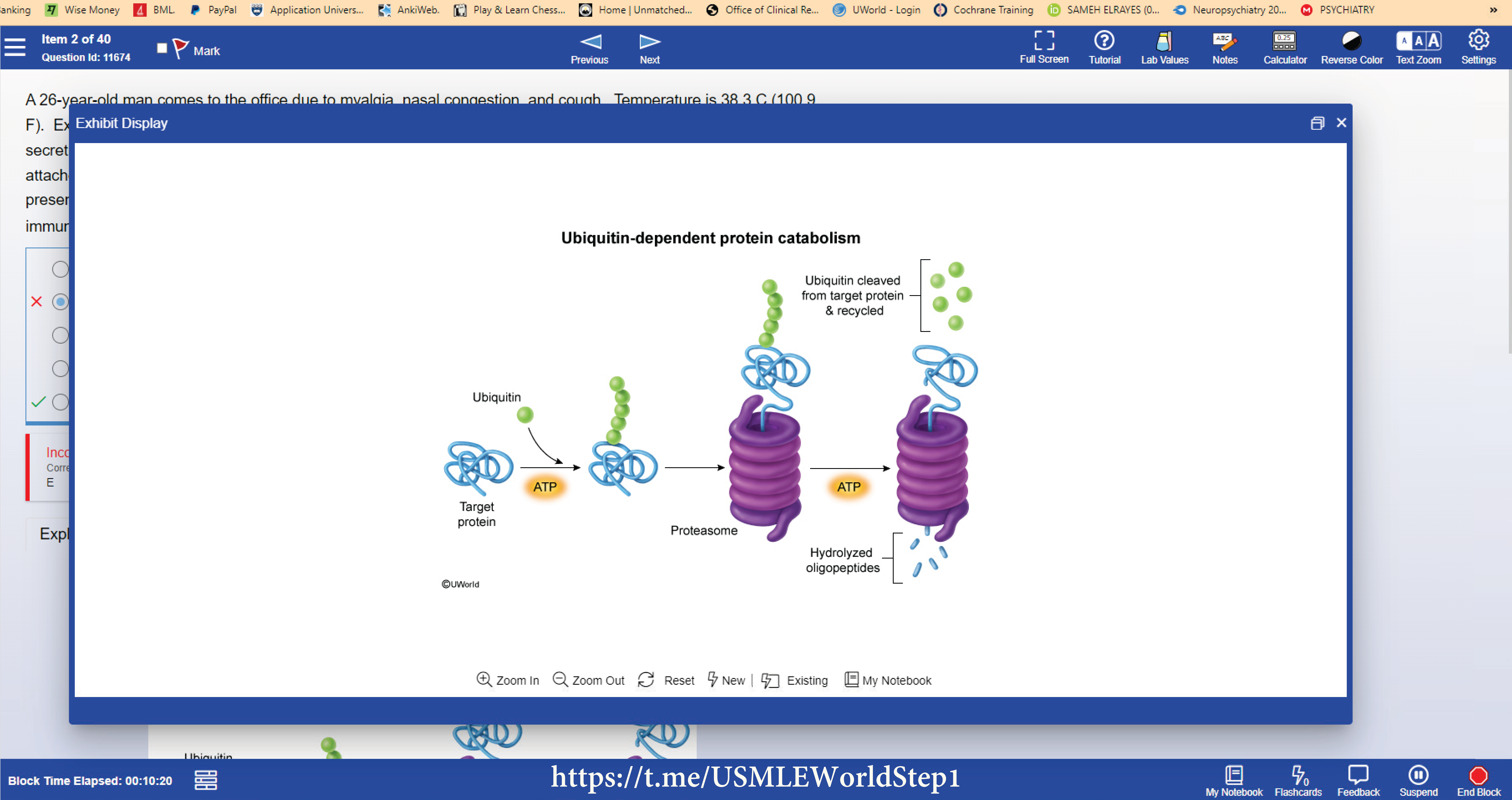
04 secs
Time Spent

2023
Version

Explanation

Ubiquitin-dependent protein catabolism

Ubiquitin cleaved from target protein & recycled
Ubiquitin
Block Time Elapsed: 00:10:20
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 40
Question Id: 11674
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9

F). Ex

secret

attach

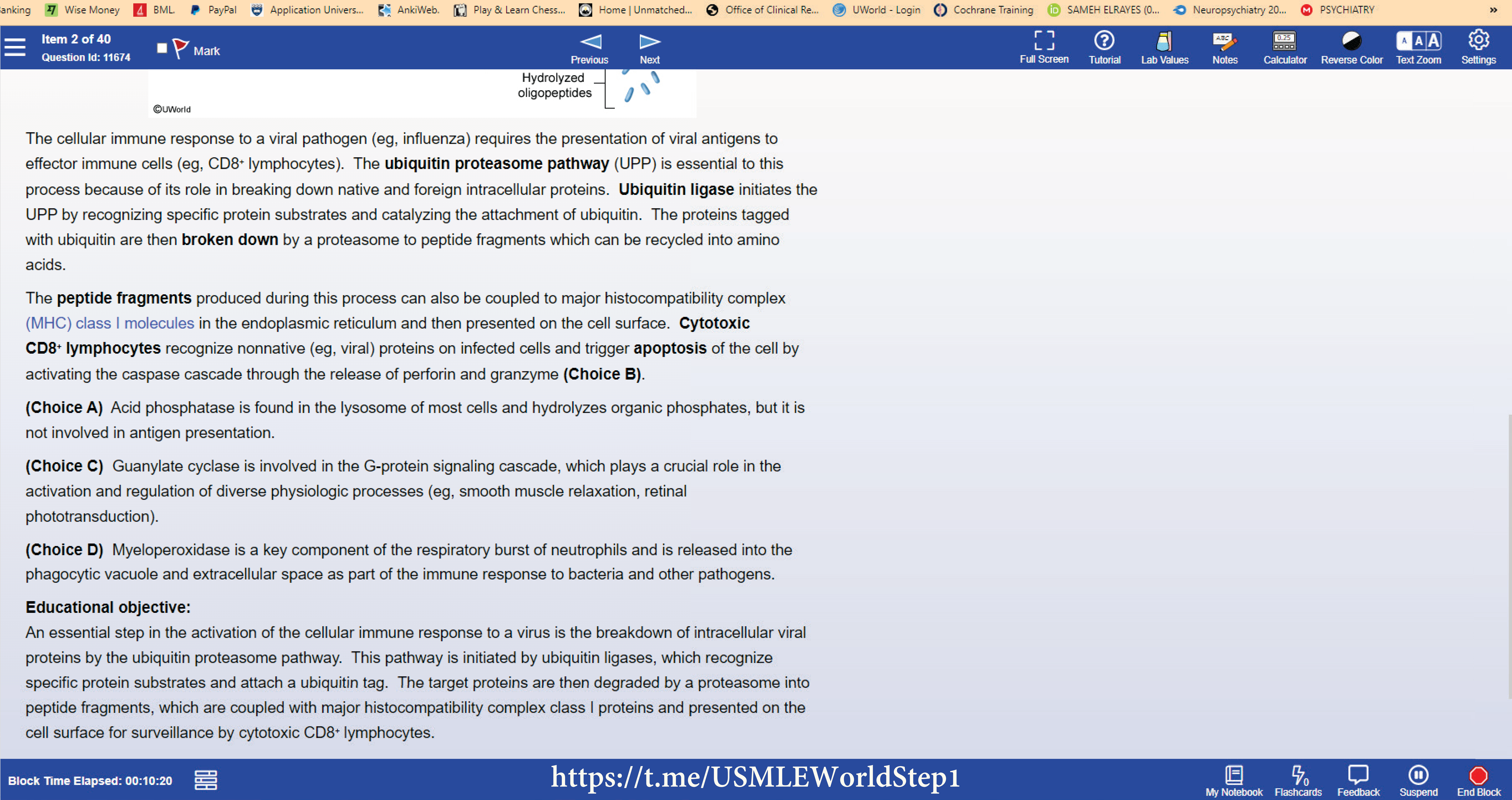
preser

immur

○
✗ ●
○
○
✓ ○
Inco
Corre
E
Expl
Exhibit Display

Ubiquitin-dependent protein catabolism

Ubiquitin cleaved
from target protein
& recycled
Ubiquitin
ATP
Target
protein
Proteasome
ATP
Hydrolyzed
oligopeptides
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Ubiquitin
Block Time Elapsed: 00:10:20
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 2 of 40
Question Id: 11674
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Hydrolyzed oligopeptides
©UWorld
Block Time Elapsed: 00:10:20
My Notebook
Flashcards
Feedback
Suspend
End Block

The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, $CD8^+$ lymphocytes). The **ubiquitin proteasome pathway** (UPP) is essential to this process because of its role in breaking down native and foreign intracellular proteins. **Ubiquitin ligase** initiates the UPP by recognizing specific protein substrates and catalyzing the attachment of ubiquitin. The proteins tagged with ubiquitin are then **broken down** by a proteasome to peptide fragments which can be recycled into amino acids.

The **peptide fragments** produced during this process can also be coupled to major histocompatibility complex (MHC) class I molecules in the endoplasmic reticulum and then presented on the cell surface. **Cytotoxic $CD8^+$ lymphocytes** recognize nonnative (eg, viral) proteins on infected cells and trigger **apoptosis** of the cell by activating the caspase cascade through the release of perforin and granzyme **(Choice B)**.

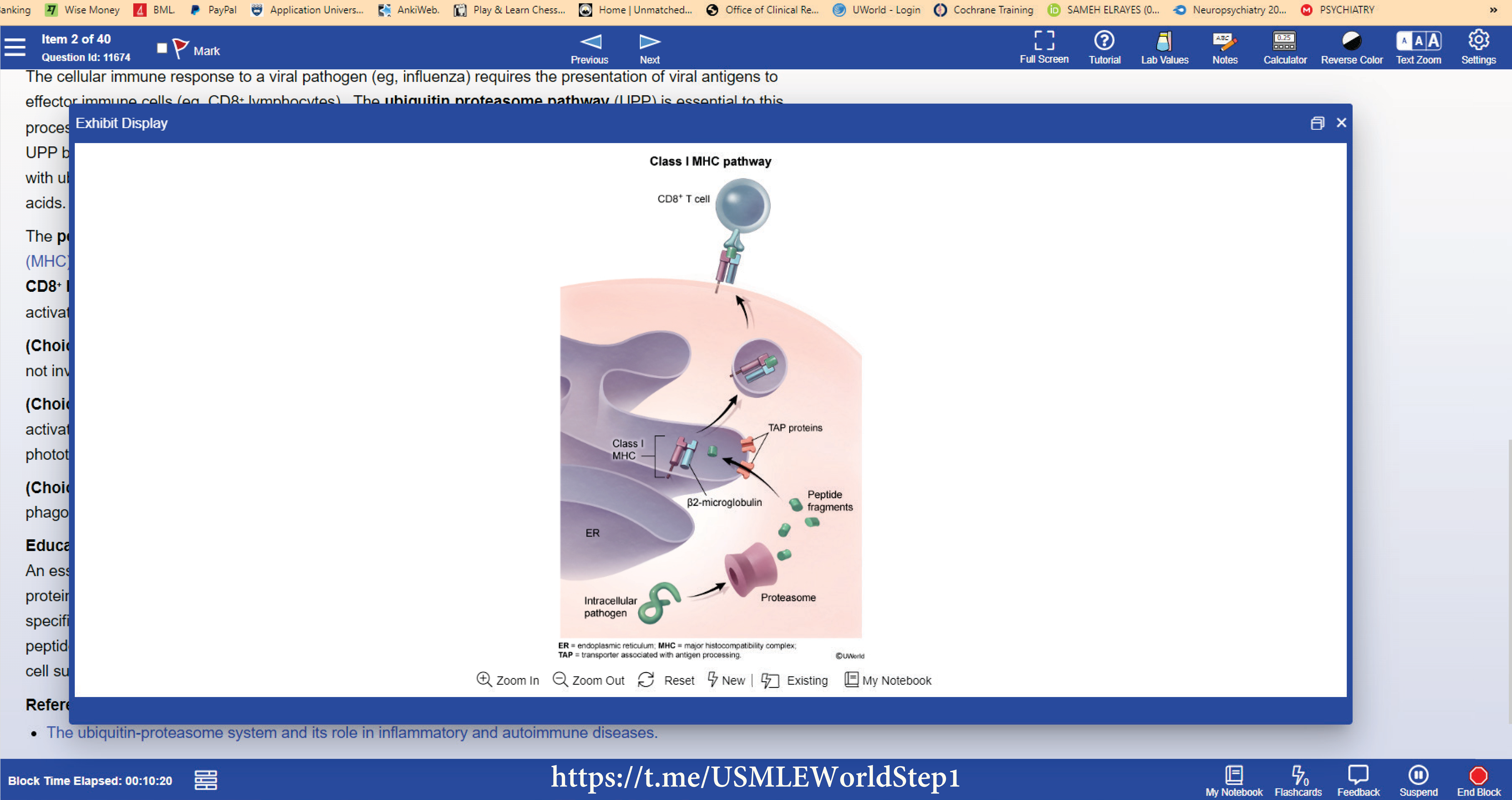
(Choice A) Acid phosphatase is found in the lysosome of most cells and hydrolyzes organic phosphates, but it is not involved in antigen presentation.

(Choice C) Guanylate cyclase is involved in the G-protein signaling cascade, which plays a crucial role in the activation and regulation of diverse physiologic processes (eg, smooth muscle relaxation, retinal phototransduction).

(Choice D) Myeloperoxidase is a key component of the respiratory burst of neutrophils and is released into the phagocytic vacuole and extracellular space as part of the immune response to bacteria and other pathogens.

Educational objective:

An essential step in the activation of the cellular immune response to a virus is the breakdown of intracellular viral proteins by the ubiquitin proteasome pathway. This pathway is initiated by ubiquitin ligases, which recognize specific protein substrates and attach a ubiquitin tag. The target proteins are then degraded by a proteasome into peptide fragments, which are coupled with major histocompatibility complex class I proteins and presented on the cell surface for surveillance by cytotoxic $CD8^+$ lymphocytes.


Item 2 of 40
Question Id: 11674
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
CD8⁺ T cell
TAP proteins
Class I MHC
β2-microglobulin
Peptide fragments
ER
Intracellular pathogen
Proteasome
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:10:20
My Notebook
Flashcards
Feedback
Suspend
End Block

The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, CD8+ lymphocytes). The **ubiquitin proteasome pathway** (UPP) is essential to this

proces

UPP b

with ub

acids.

The **p**

(MHC)

CD8+ l

activat

(Choi

not inv

(Choi

activat

photot

(Choi

phago

Educa

An ess

protein

specifi

peptid

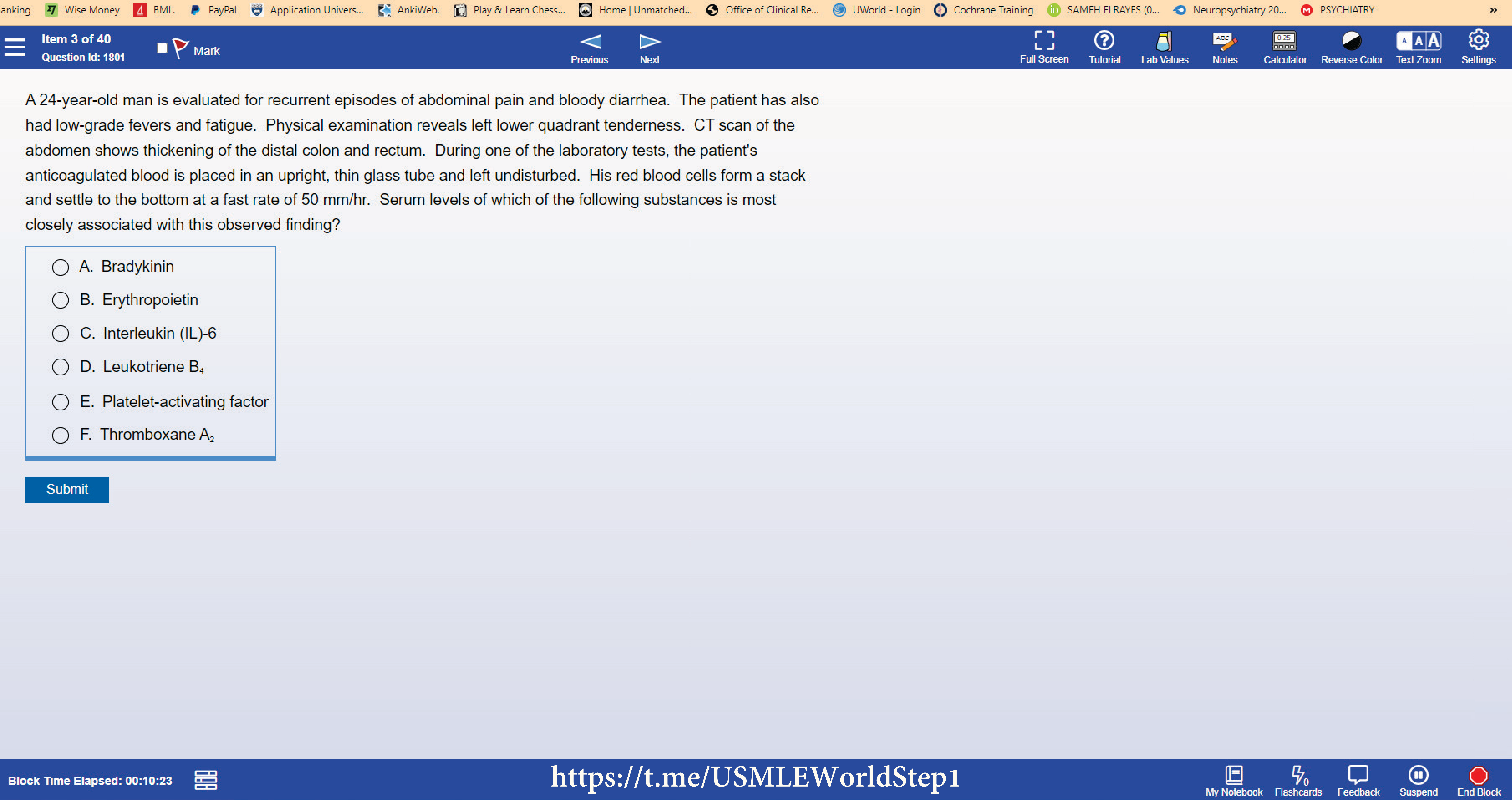
cell su

Refere

- The ubiquitin-proteasome system and its role in inflammatory and autoimmune diseases.

Class I MHC pathway

ER = endoplasmic reticulum; **MHC** = major histocompatibility complex; **TAP** = transporter associated with antigen processing.

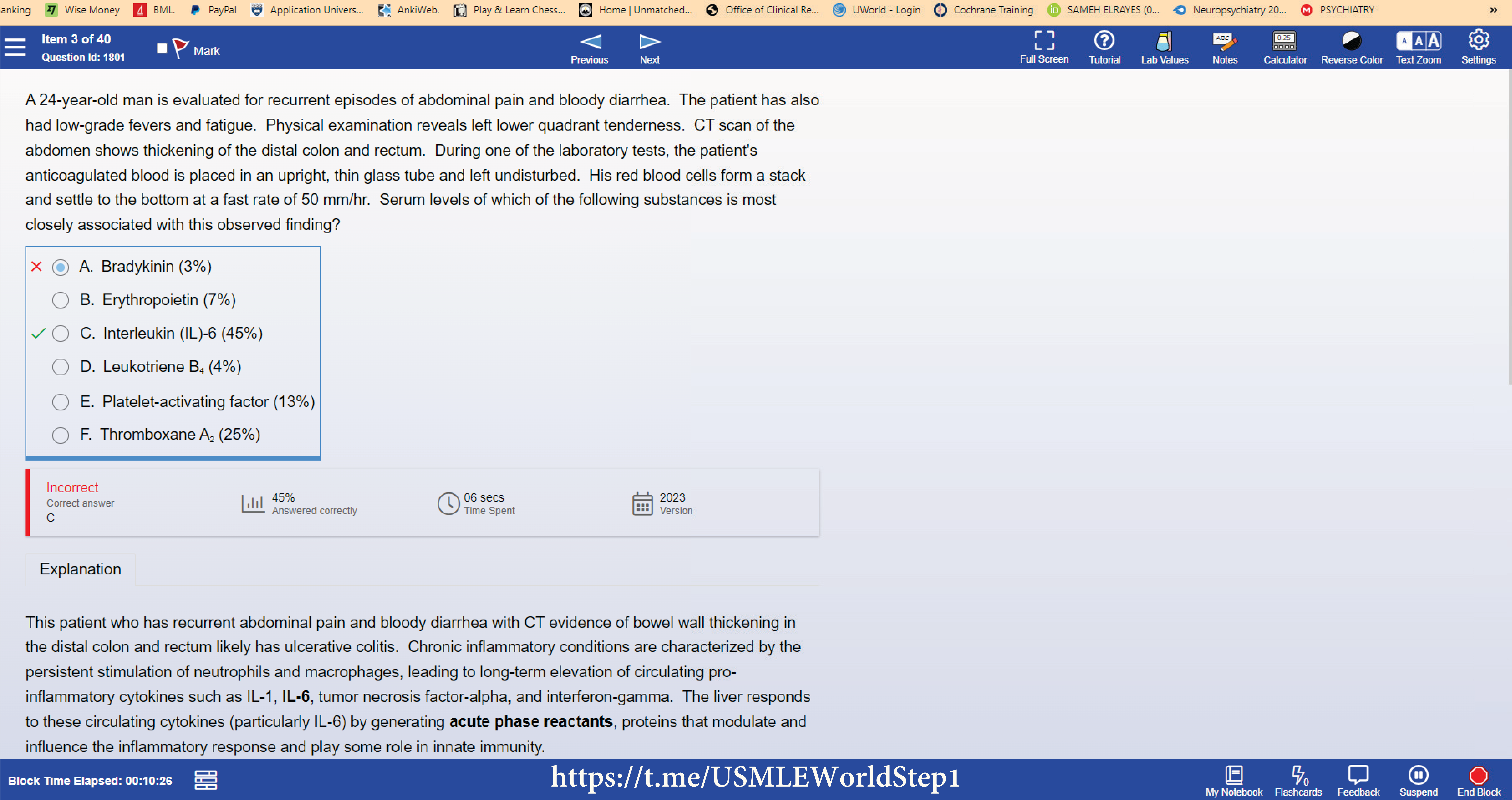

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 3 of 40
Question Id: 1801

A 24-year-old man is evaluated for recurrent episodes of abdominal pain and bloody diarrhea. The patient has also had low-grade fevers and fatigue. Physical examination reveals left lower quadrant tenderness. CT scan of the abdomen shows thickening of the distal colon and rectum. During one of the laboratory tests, the patient's anticoagulated blood is placed in an upright, thin glass tube and left undisturbed. His red blood cells form a stack and settle to the bottom at a fast rate of 50 mm/hr. Serum levels of which of the following substances is most closely associated with this observed finding?

○ A. Bradykinin
○ B. Erythropoietin
○ C. Interleukin (IL)-6
○ D. Leukotriene B_4
○ E. Platelet-activating factor
○ F. Thromboxane A_2

Block Time Elapsed: 00:10:23


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 3 of 40
Question Id: 1801
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 24-year-old man is evaluated for recurrent episodes of abdominal pain and bloody diarrhea. The patient has also had low-grade fevers and fatigue. Physical examination reveals left lower quadrant tenderness. CT scan of the abdomen shows thickening of the distal colon and rectum. During one of the laboratory tests, the patient's anticoagulated blood is placed in an upright, thin glass tube and left undisturbed. His red blood cells form a stack and settle to the bottom at a fast rate of 50 mm/hr. Serum levels of which of the following substances is most closely associated with this observed finding?

- ✗ ● A. Bradykinin (3%)
- ○ B. Erythropoietin (7%)
- ✓ ○ C. Interleukin (IL)-6 (45%)
- ○ D. Leukotriene B$_4$ (4%)
- ○ E. Platelet-activating factor (13%)
- ○ F. Thromboxane A$_2$ (25%)

Incorrect
Correct answer
C

45%
Answered correctly

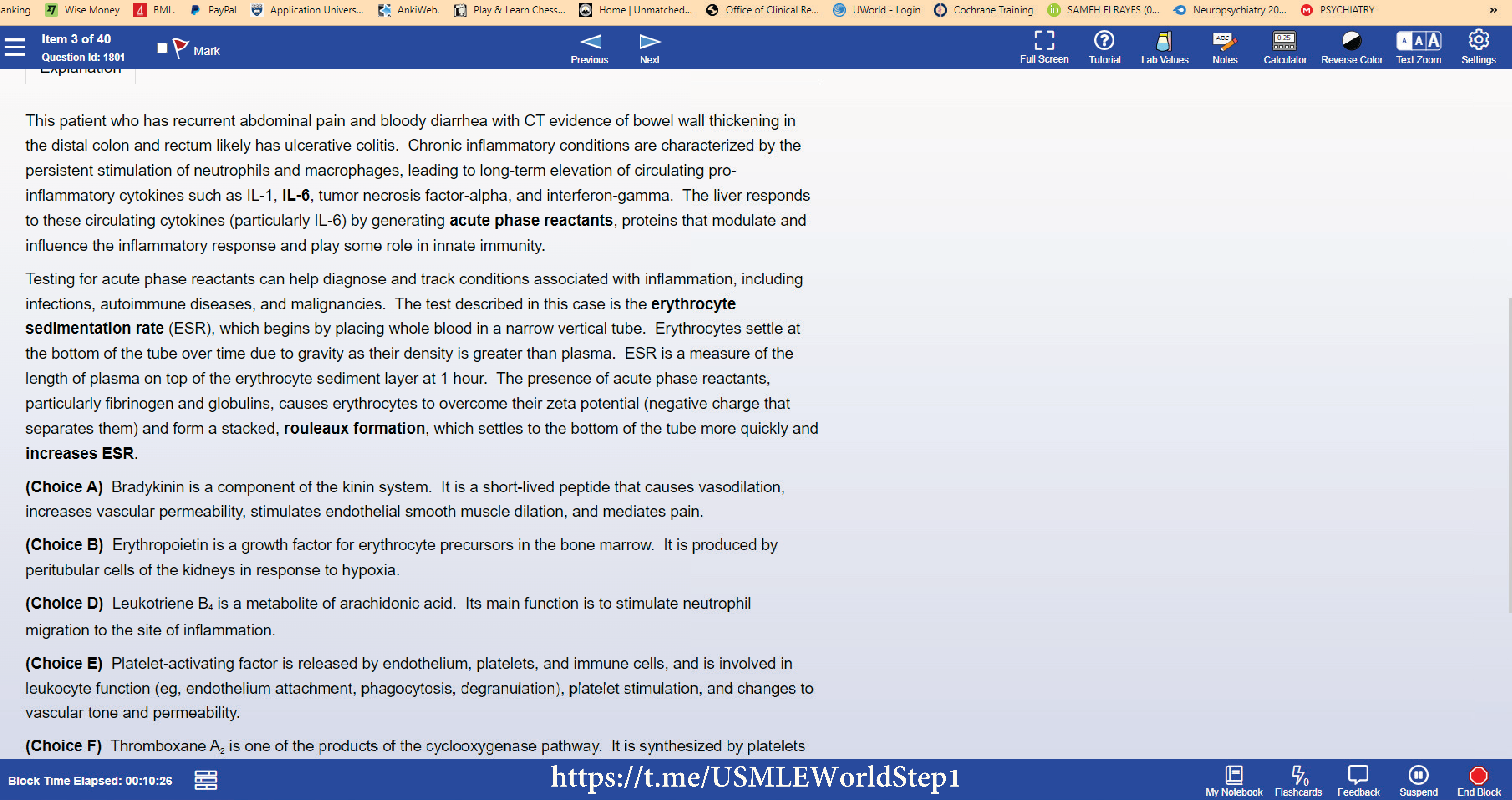
06 secs
Time Spent

2023
Version

Explanation

This patient who has recurrent abdominal pain and bloody diarrhea with CT evidence of bowel wall thickening in the distal colon and rectum likely has ulcerative colitis. Chronic inflammatory conditions are characterized by the persistent stimulation of neutrophils and macrophages, leading to long-term elevation of circulating pro-inflammatory cytokines such as IL-1, **IL-6**, tumor necrosis factor-alpha, and interferon-gamma. The liver responds to these circulating cytokines (particularly IL-6) by generating **acute phase reactants**, proteins that modulate and influence the inflammatory response and play some role in innate immunity.

Block Time Elapsed: 00:10:26
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 3 of 40
Question Id: 1801
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

This patient who has recurrent abdominal pain and bloody diarrhea with CT evidence of bowel wall thickening in the distal colon and rectum likely has ulcerative colitis. Chronic inflammatory conditions are characterized by the persistent stimulation of neutrophils and macrophages, leading to long-term elevation of circulating pro-inflammatory cytokines such as IL-1, **IL-6**, tumor necrosis factor-alpha, and interferon-gamma. The liver responds to these circulating cytokines (particularly IL-6) by generating **acute phase reactants**, proteins that modulate and influence the inflammatory response and play some role in innate immunity.

Testing for acute phase reactants can help diagnose and track conditions associated with inflammation, including infections, autoimmune diseases, and malignancies. The test described in this case is the **erythrocyte sedimentation rate** (ESR), which begins by placing whole blood in a narrow vertical tube. Erythrocytes settle at the bottom of the tube over time due to gravity as their density is greater than plasma. ESR is a measure of the length of plasma on top of the erythrocyte sediment layer at 1 hour. The presence of acute phase reactants, particularly fibrinogen and globulins, causes erythrocytes to overcome their zeta potential (negative charge that separates them) and form a stacked, **rouleaux formation**, which settles to the bottom of the tube more quickly and **increases ESR**.

(Choice A) Bradykinin is a component of the kinin system. It is a short-lived peptide that causes vasodilation, increases vascular permeability, stimulates endothelial smooth muscle dilation, and mediates pain.

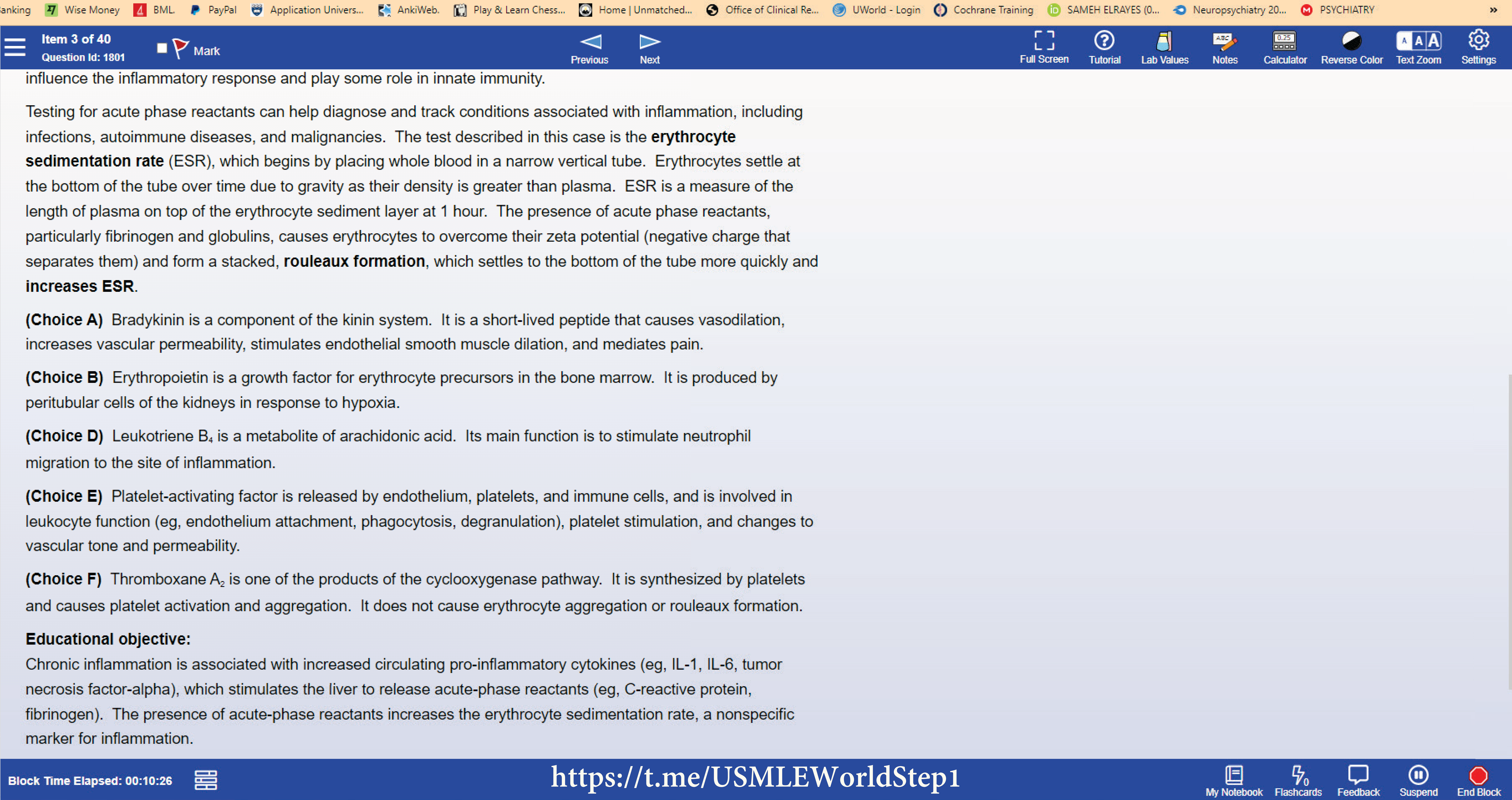
(Choice B) Erythropoietin is a growth factor for erythrocyte precursors in the bone marrow. It is produced by peritubular cells of the kidneys in response to hypoxia.

(Choice D) Leukotriene B_4 is a metabolite of arachidonic acid. Its main function is to stimulate neutrophil migration to the site of inflammation.

(Choice E) Platelet-activating factor is released by endothelium, platelets, and immune cells, and is involved in leukocyte function (eg, endothelium attachment, phagocytosis, degranulation), platelet stimulation, and changes to vascular tone and permeability.

(Choice F) Thromboxane A_2 is one of the products of the cyclooxygenase pathway. It is synthesized by platelets

Block Time Elapsed: 00:10:26
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 3 of 40
Question Id: 1801
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

influence the inflammatory response and play some role in innate immunity.

Testing for acute phase reactants can help diagnose and track conditions associated with inflammation, including infections, autoimmune diseases, and malignancies. The test described in this case is the **erythrocyte sedimentation rate** (ESR), which begins by placing whole blood in a narrow vertical tube. Erythrocytes settle at the bottom of the tube over time due to gravity as their density is greater than plasma. ESR is a measure of the length of plasma on top of the erythrocyte sediment layer at 1 hour. The presence of acute phase reactants, particularly fibrinogen and globulins, causes erythrocytes to overcome their zeta potential (negative charge that separates them) and form a stacked, **rouleaux formation**, which settles to the bottom of the tube more quickly and **increases ESR**.

(Choice A) Bradykinin is a component of the kinin system. It is a short-lived peptide that causes vasodilation, increases vascular permeability, stimulates endothelial smooth muscle dilation, and mediates pain.

(Choice B) Erythropoietin is a growth factor for erythrocyte precursors in the bone marrow. It is produced by peritubular cells of the kidneys in response to hypoxia.

(Choice D) Leukotriene B_4 is a metabolite of arachidonic acid. Its main function is to stimulate neutrophil migration to the site of inflammation.

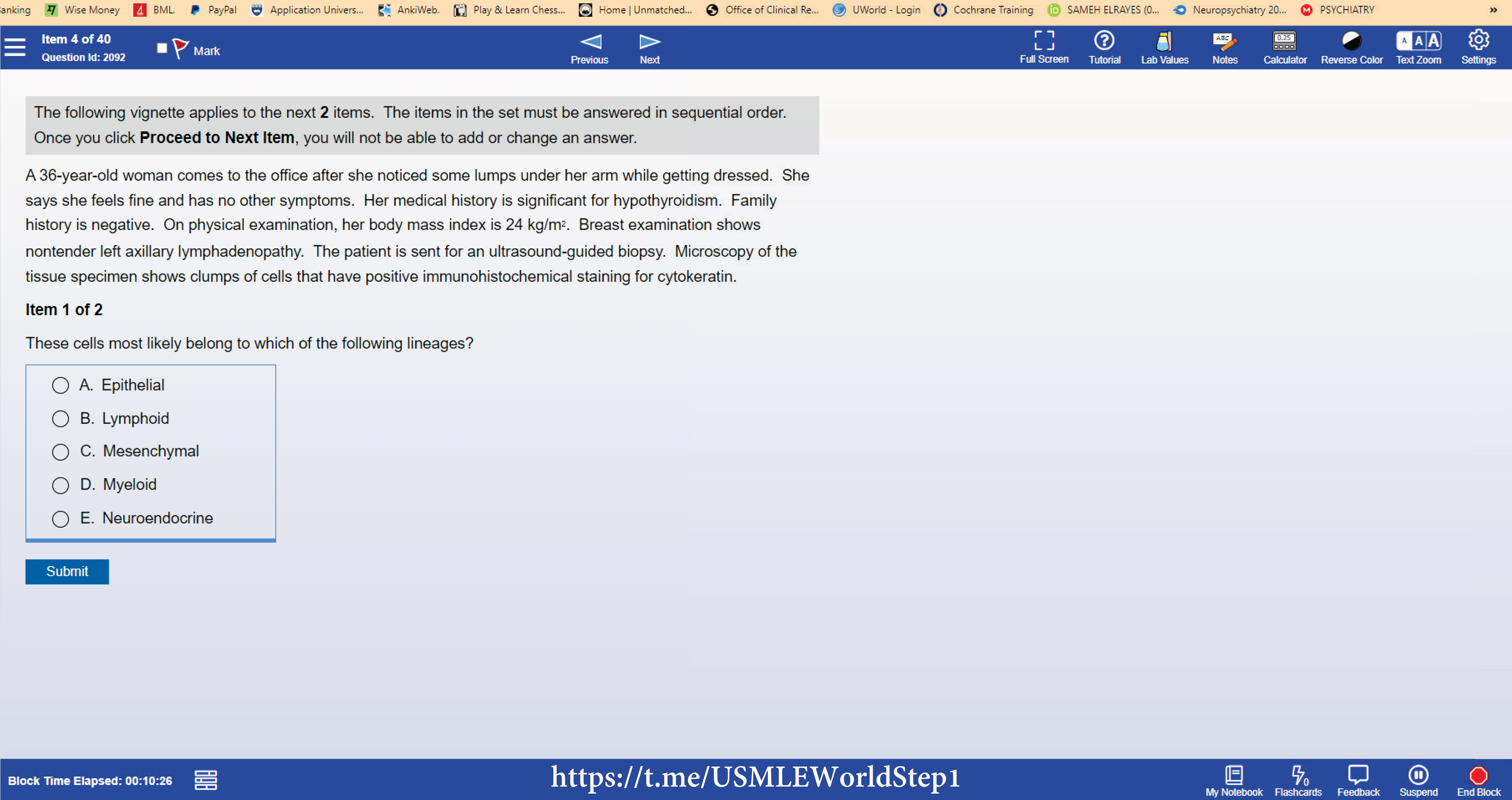
(Choice E) Platelet-activating factor is released by endothelium, platelets, and immune cells, and is involved in leukocyte function (eg, endothelium attachment, phagocytosis, degranulation), platelet stimulation, and changes to vascular tone and permeability.

(Choice F) Thromboxane A_2 is one of the products of the cyclooxygenase pathway. It is synthesized by platelets and causes platelet activation and aggregation. It does not cause erythrocyte aggregation or rouleaux formation.

Educational objective:

Chronic inflammation is associated with increased circulating pro-inflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha), which stimulates the liver to release acute-phase reactants (eg, C-reactive protein, fibrinogen). The presence of acute-phase reactants increases the erythrocyte sedimentation rate, a nonspecific marker for inflammation.

Block Time Elapsed: 00:10:26
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 4 of 40
Question Id: 2092
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

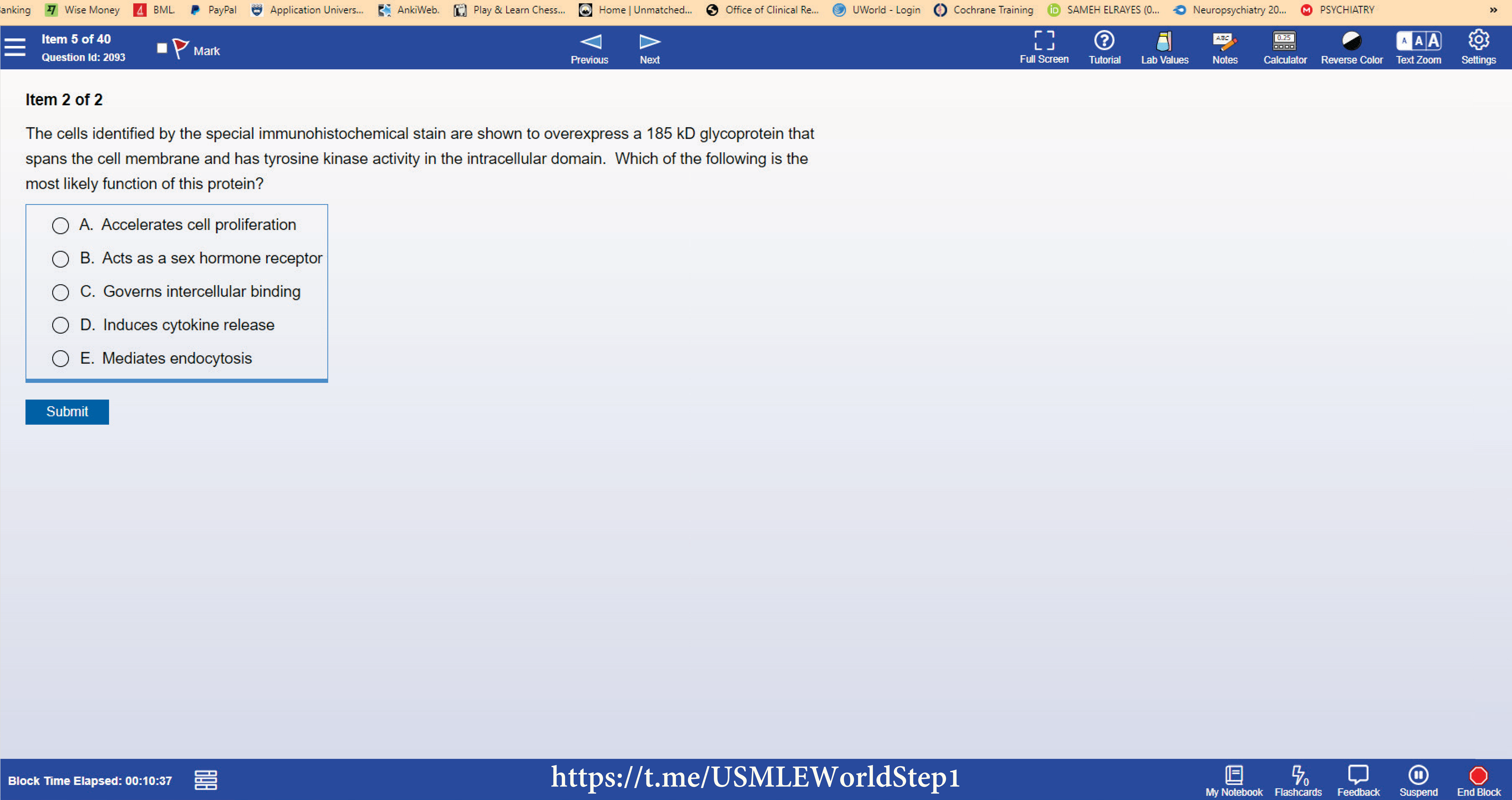
A 36-year-old woman comes to the office after she noticed some lumps under her arm while getting dressed. She says she feels fine and has no other symptoms. Her medical history is significant for hypothyroidism. Family history is negative. On physical examination, her body mass index is 24 kg/m^2. Breast examination shows nontender left axillary lymphadenopathy. The patient is sent for an ultrasound-guided biopsy. Microscopy of the tissue specimen shows clumps of cells that have positive immunohistochemical staining for cytokeratin.

Item 1 of 2

These cells most likely belong to which of the following lineages?

○ A. Epithelial
○ B. Lymphoid
○ C. Mesenchymal
○ D. Myeloid
○ E. Neuroendocrine

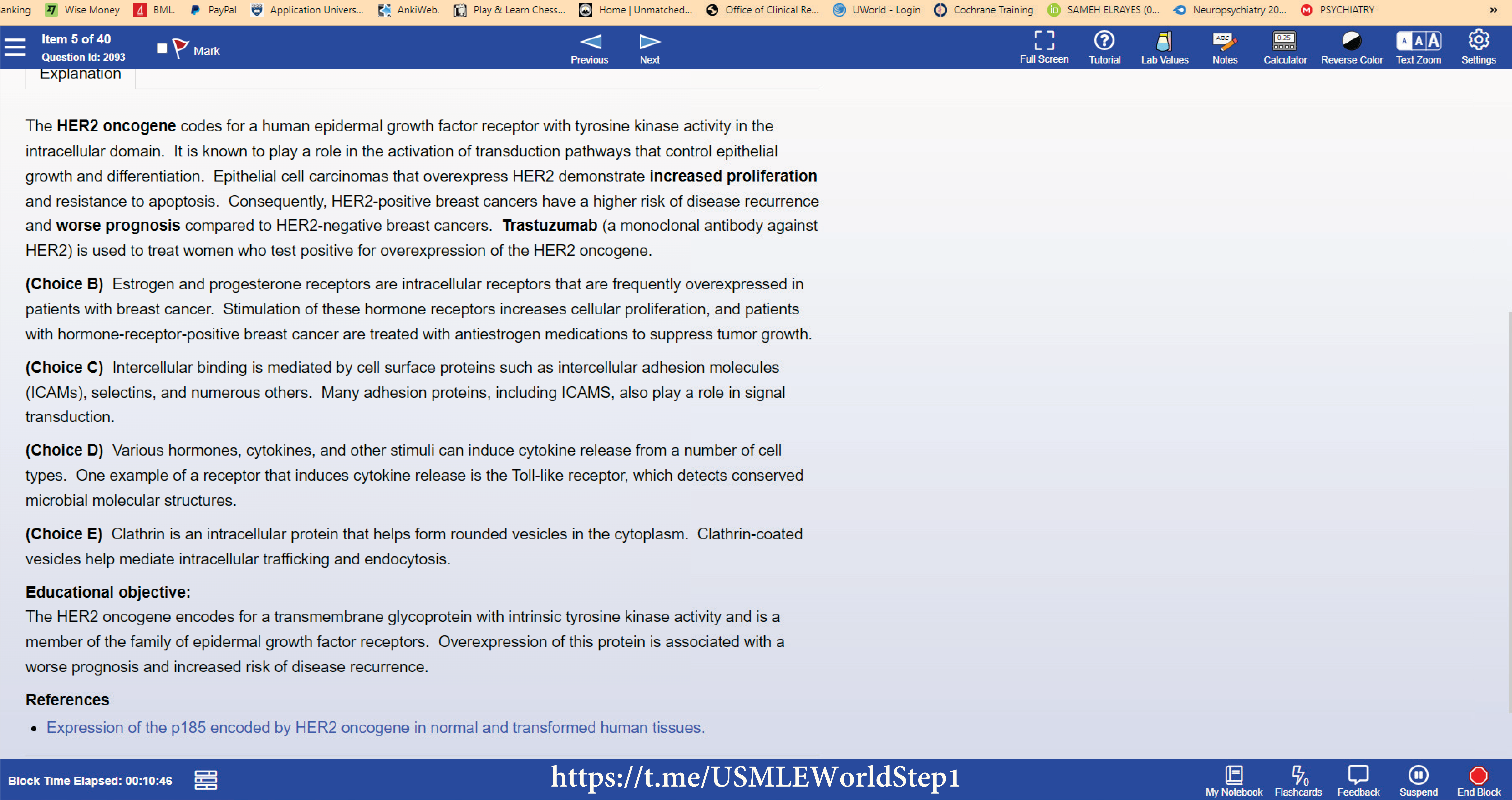
Submit
Block Time Elapsed: 00:10:26
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 5 of 40
Question Id: 2093
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:10:37
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 2 of 2

The cells identified by the special immunohistochemical stain are shown to overexpress a 185 kD glycoprotein that spans the cell membrane and has tyrosine kinase activity in the intracellular domain. Which of the following is the most likely function of this protein?

○ A. Accelerates cell proliferation
○ B. Acts as a sex hormone receptor
○ C. Governs intercellular binding
○ D. Induces cytokine release
○ E. Mediates endocytosis


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 5 of 40
Question Id: 2093
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:10:46
My Notebook
Flashcards
Feedback
Suspend
End Block

The **HER2 oncogene** codes for a human epidermal growth factor receptor with tyrosine kinase activity in the intracellular domain. It is known to play a role in the activation of transduction pathways that control epithelial growth and differentiation. Epithelial cell carcinomas that overexpress HER2 demonstrate **increased proliferation** and resistance to apoptosis. Consequently, HER2-positive breast cancers have a higher risk of disease recurrence and **worse prognosis** compared to HER2-negative breast cancers. **Trastuzumab** (a monoclonal antibody against HER2) is used to treat women who test positive for overexpression of the HER2 oncogene.

(Choice B) Estrogen and progesterone receptors are intracellular receptors that are frequently overexpressed in patients with breast cancer. Stimulation of these hormone receptors increases cellular proliferation, and patients with hormone-receptor-positive breast cancer are treated with antiestrogen medications to suppress tumor growth.

(Choice C) Intercellular binding is mediated by cell surface proteins such as intercellular adhesion molecules (ICAMs), selectins, and numerous others. Many adhesion proteins, including ICAMS, also play a role in signal transduction.

(Choice D) Various hormones, cytokines, and other stimuli can induce cytokine release from a number of cell types. One example of a receptor that induces cytokine release is the Toll-like receptor, which detects conserved microbial molecular structures.

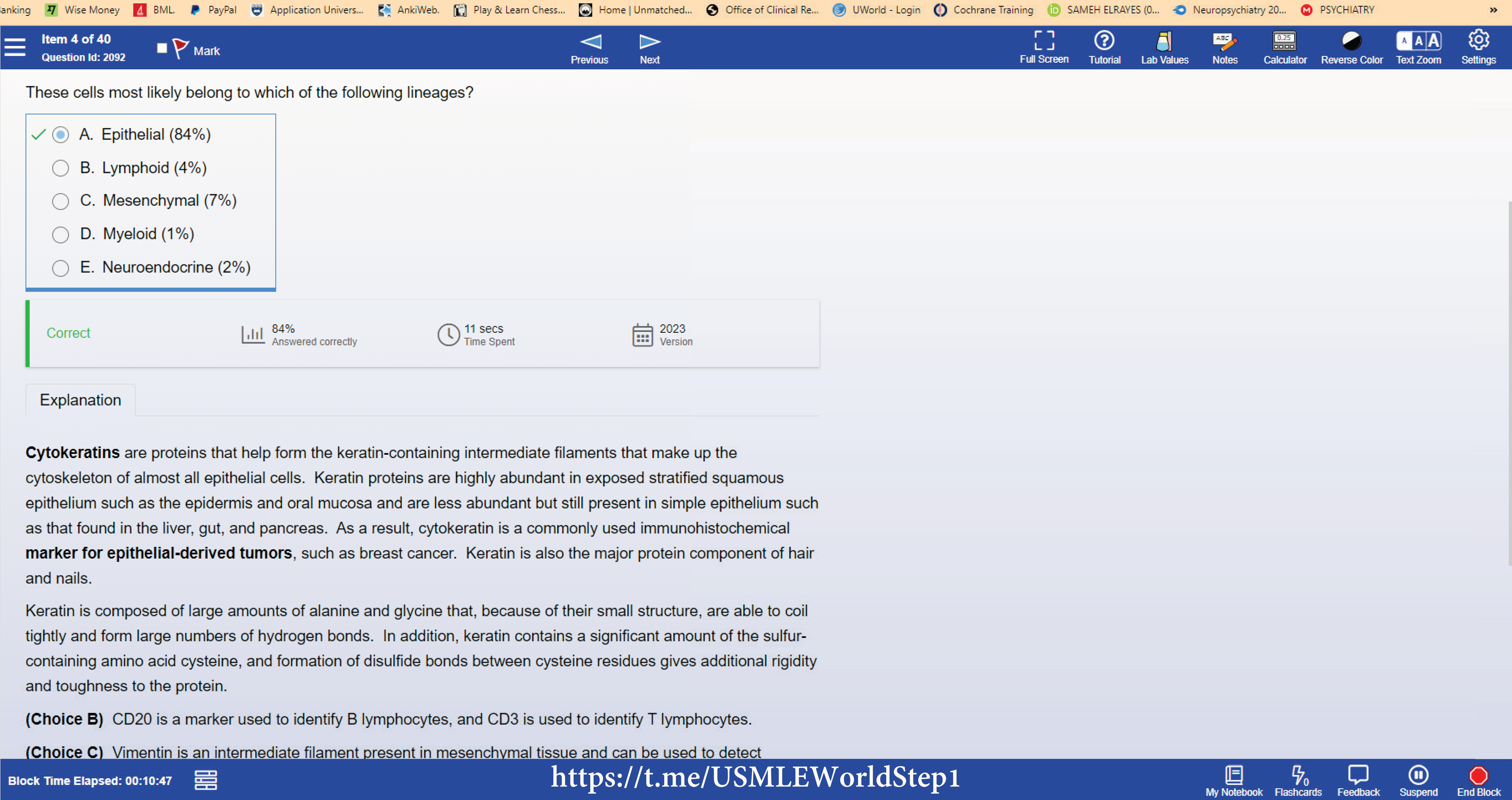
(Choice E) Clathrin is an intracellular protein that helps form rounded vesicles in the cytoplasm. Clathrin-coated vesicles help mediate intracellular trafficking and endocytosis.

Educational objective:

The HER2 oncogene encodes for a transmembrane glycoprotein with intrinsic tyrosine kinase activity and is a member of the family of epidermal growth factor receptors. Overexpression of this protein is associated with a worse prognosis and increased risk of disease recurrence.

References

- Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues.


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 4 of 40
Question Id: 2092
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

These cells most likely belong to which of the following lineages?

✓ ● A. Epithelial (84%)
○ B. Lymphoid (4%)
○ C. Mesenchymal (7%)
○ D. Myeloid (1%)
○ E. Neuroendocrine (2%)

Correct
84% Answered correctly
11 secs Time Spent
2023 Version

Explanation

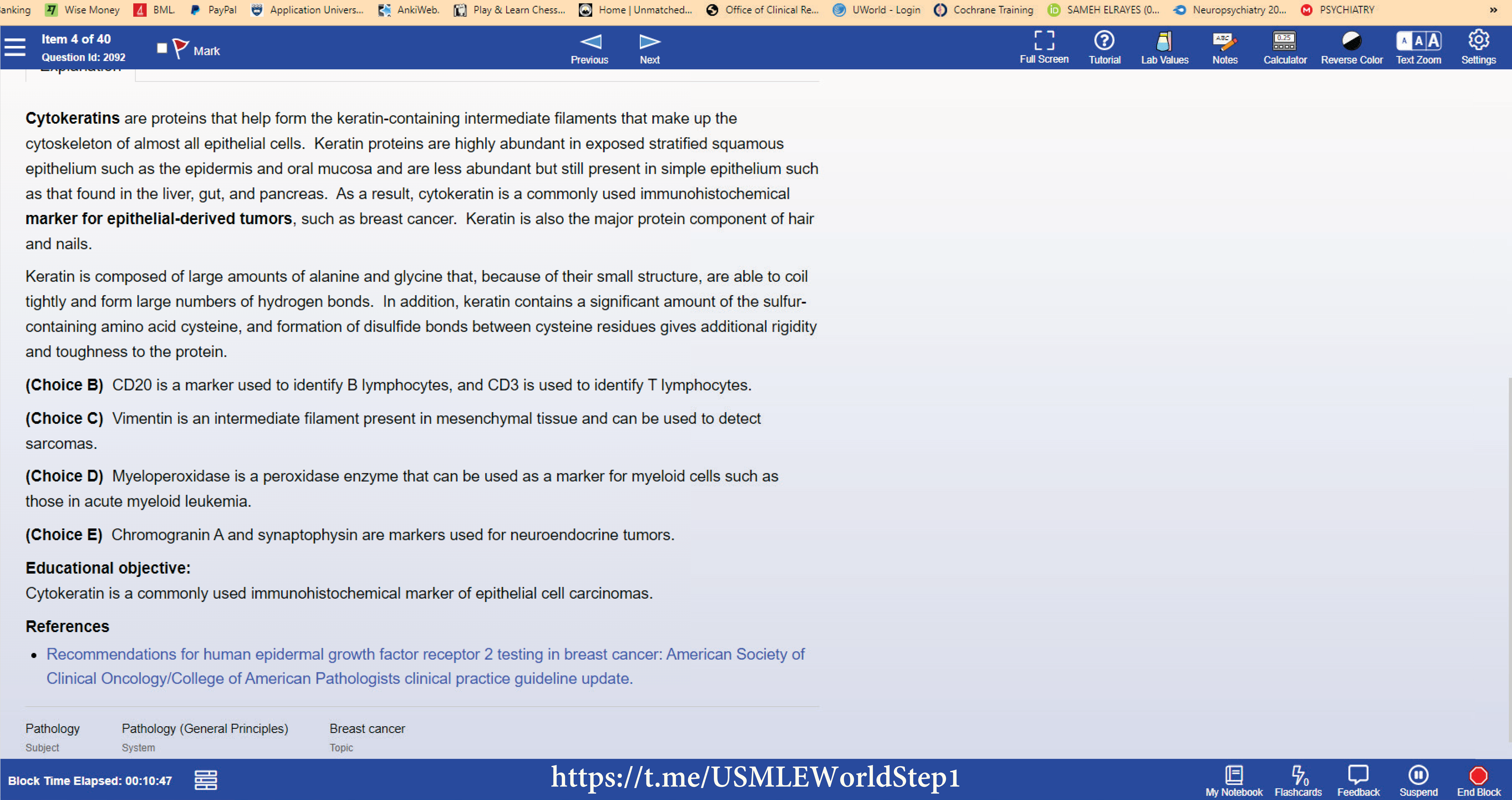
Cytokeratins are proteins that help form the keratin-containing intermediate filaments that make up the cytoskeleton of almost all epithelial cells. Keratin proteins are highly abundant in exposed stratified squamous epithelium such as the epidermis and oral mucosa and are less abundant but still present in simple epithelium such as that found in the liver, gut, and pancreas. As a result, cytokeratin is a commonly used immunohistochemical **marker for epithelial-derived tumors**, such as breast cancer. Keratin is also the major protein component of hair and nails.

Keratin is composed of large amounts of alanine and glycine that, because of their small structure, are able to coil tightly and form large numbers of hydrogen bonds. In addition, keratin contains a significant amount of the sulfur-containing amino acid cysteine, and formation of disulfide bonds between cysteine residues gives additional rigidity and toughness to the protein.

(Choice B) CD20 is a marker used to identify B lymphocytes, and CD3 is used to identify T lymphocytes.

(Choice C) Vimentin is an intermediate filament present in mesenchymal tissue and can be used to detect

Block Time Elapsed: 00:10:47
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 4 of 40
Question Id: 2092
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Cytokeratins are proteins that help form the keratin-containing intermediate filaments that make up the cytoskeleton of almost all epithelial cells. Keratin proteins are highly abundant in exposed stratified squamous epithelium such as the epidermis and oral mucosa and are less abundant but still present in simple epithelium such as that found in the liver, gut, and pancreas. As a result, cytokeratin is a commonly used immunohistochemical **marker for epithelial-derived tumors**, such as breast cancer. Keratin is also the major protein component of hair and nails.

Keratin is composed of large amounts of alanine and glycine that, because of their small structure, are able to coil tightly and form large numbers of hydrogen bonds. In addition, keratin contains a significant amount of the sulfur-containing amino acid cysteine, and formation of disulfide bonds between cysteine residues gives additional rigidity and toughness to the protein.

(Choice B) CD20 is a marker used to identify B lymphocytes, and CD3 is used to identify T lymphocytes.

(Choice C) Vimentin is an intermediate filament present in mesenchymal tissue and can be used to detect sarcomas.

(Choice D) Myeloperoxidase is a peroxidase enzyme that can be used as a marker for myeloid cells such as those in acute myeloid leukemia.

(Choice E) Chromogranin A and synaptophysin are markers used for neuroendocrine tumors.

Educational objective:
Cytokeratin is a commonly used immunohistochemical marker of epithelial cell carcinomas.

References

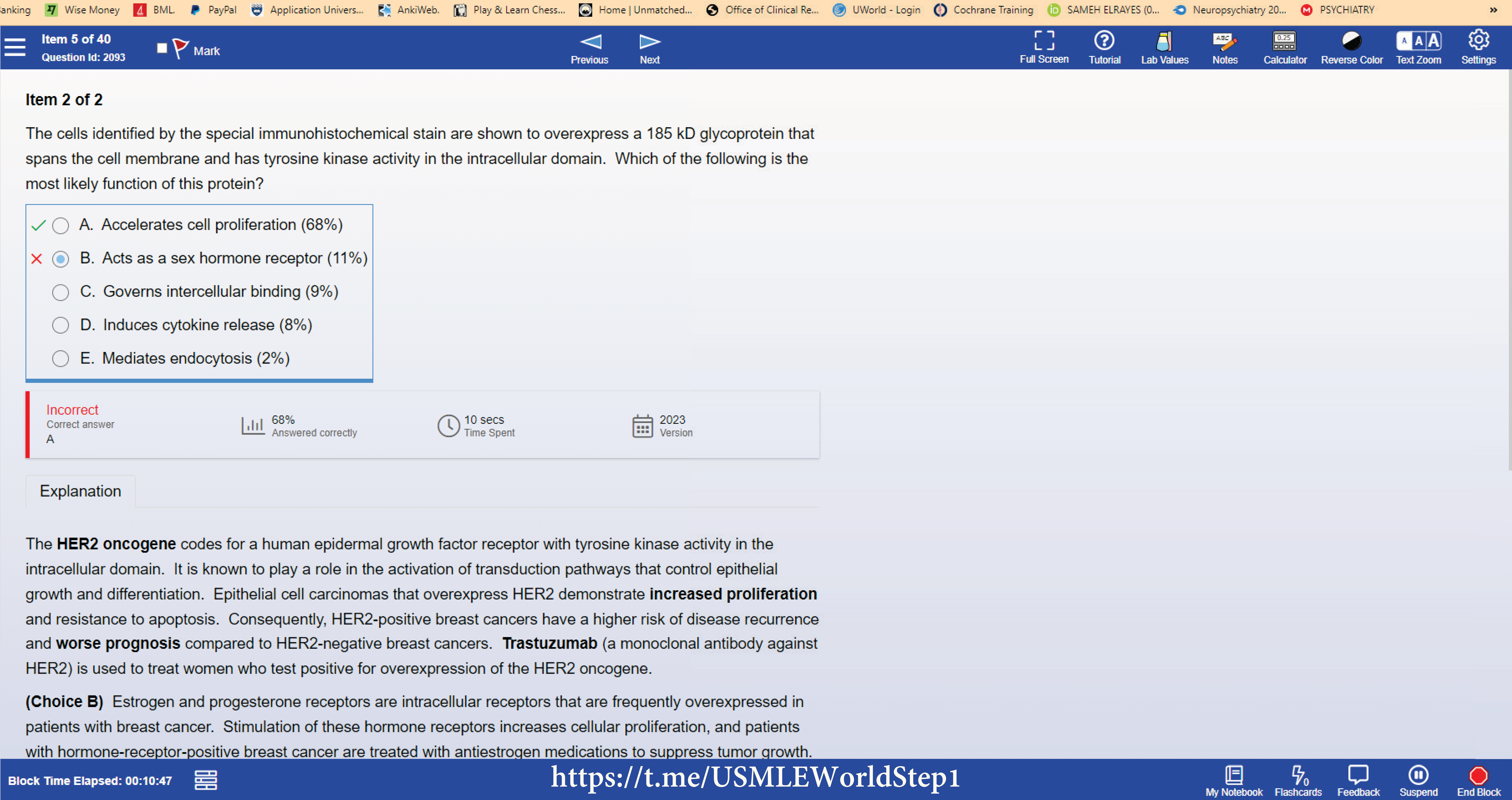
- Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.

Pathology	Pathology (General Principles)	Breast cancer
Subject	System	Topic

Block Time Elapsed: 00:10:47

https://t.me/USMLEWorldStep1

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 5 of 40
Question Id: 2093
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:10:47
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 2 of 2

The cells identified by the special immunohistochemical stain are shown to overexpress a 185 kD glycoprotein that spans the cell membrane and has tyrosine kinase activity in the intracellular domain. Which of the following is the most likely function of this protein?

- ✓ ○ A. Accelerates cell proliferation (68%)
- ✗ ● B. Acts as a sex hormone receptor (11%)
- ○ C. Governs intercellular binding (9%)
- ○ D. Induces cytokine release (8%)
- ○ E. Mediates endocytosis (2%)

Incorrect
Correct answer
A

68%
Answered correctly

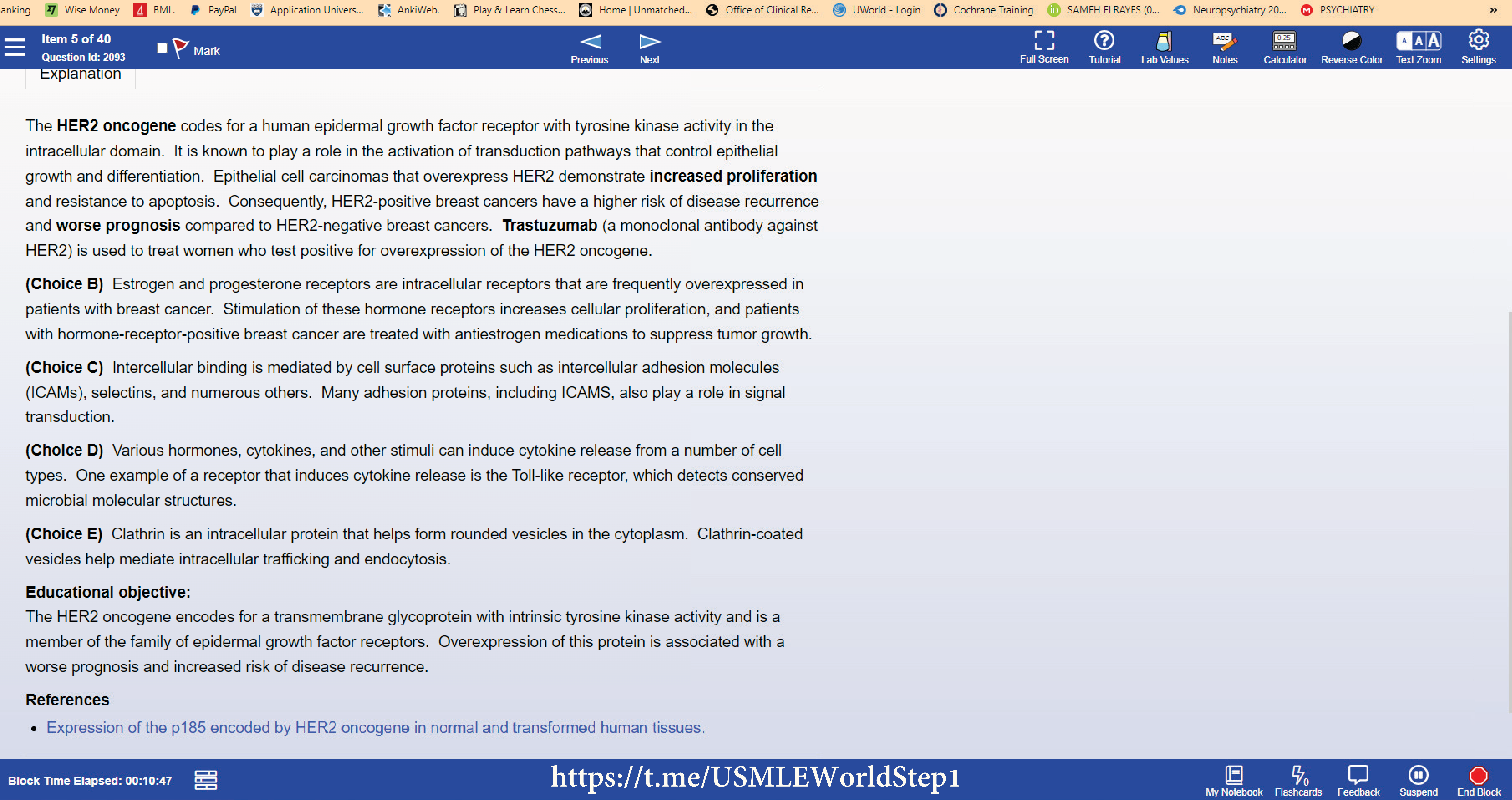
10 secs
Time Spent

2023
Version

Explanation

The **HER2 oncogene** codes for a human epidermal growth factor receptor with tyrosine kinase activity in the intracellular domain. It is known to play a role in the activation of transduction pathways that control epithelial growth and differentiation. Epithelial cell carcinomas that overexpress HER2 demonstrate **increased proliferation** and resistance to apoptosis. Consequently, HER2-positive breast cancers have a higher risk of disease recurrence and **worse prognosis** compared to HER2-negative breast cancers. **Trastuzumab** (a monoclonal antibody against HER2) is used to treat women who test positive for overexpression of the HER2 oncogene.

(Choice B) Estrogen and progesterone receptors are intracellular receptors that are frequently overexpressed in patients with breast cancer. Stimulation of these hormone receptors increases cellular proliferation, and patients with hormone-receptor-positive breast cancer are treated with antiestrogen medications to suppress tumor growth.


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 5 of 40
Question Id: 2093
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

The **HER2 oncogene** codes for a human epidermal growth factor receptor with tyrosine kinase activity in the intracellular domain. It is known to play a role in the activation of transduction pathways that control epithelial growth and differentiation. Epithelial cell carcinomas that overexpress HER2 demonstrate **increased proliferation** and resistance to apoptosis. Consequently, HER2-positive breast cancers have a higher risk of disease recurrence and **worse prognosis** compared to HER2-negative breast cancers. **Trastuzumab** (a monoclonal antibody against HER2) is used to treat women who test positive for overexpression of the HER2 oncogene.

(Choice B) Estrogen and progesterone receptors are intracellular receptors that are frequently overexpressed in patients with breast cancer. Stimulation of these hormone receptors increases cellular proliferation, and patients with hormone-receptor-positive breast cancer are treated with antiestrogen medications to suppress tumor growth.

(Choice C) Intercellular binding is mediated by cell surface proteins such as intercellular adhesion molecules (ICAMs), selectins, and numerous others. Many adhesion proteins, including ICAMS, also play a role in signal transduction.

(Choice D) Various hormones, cytokines, and other stimuli can induce cytokine release from a number of cell types. One example of a receptor that induces cytokine release is the Toll-like receptor, which detects conserved microbial molecular structures.

(Choice E) Clathrin is an intracellular protein that helps form rounded vesicles in the cytoplasm. Clathrin-coated vesicles help mediate intracellular trafficking and endocytosis.

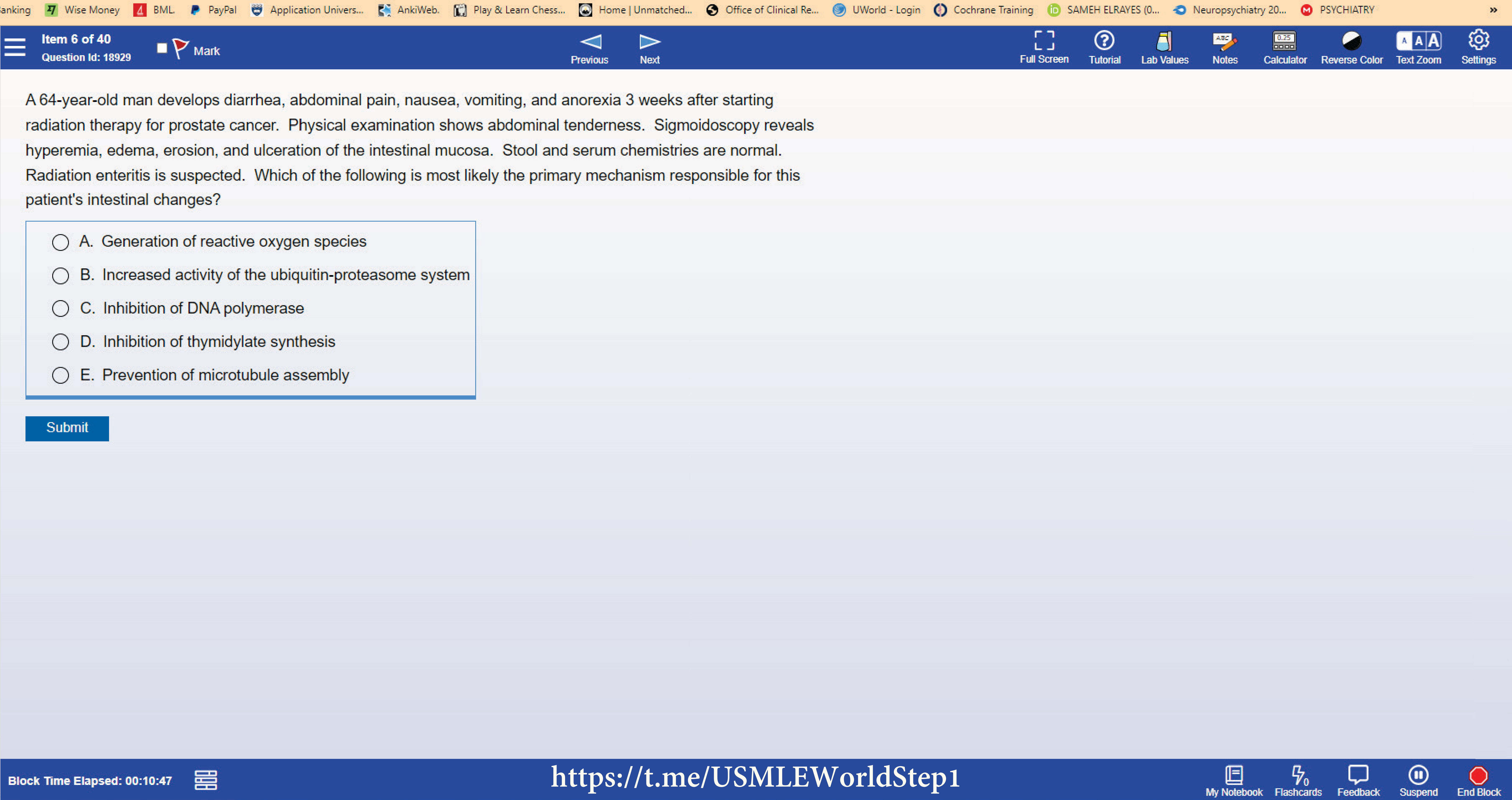
Educational objective:

The HER2 oncogene encodes for a transmembrane glycoprotein with intrinsic tyrosine kinase activity and is a member of the family of epidermal growth factor receptors. Overexpression of this protein is associated with a worse prognosis and increased risk of disease recurrence.

References

- Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues.

Block Time Elapsed: 00:10:47
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Item 6 of 40
Question Id: 18929

A 64-year-old man develops diarrhea, abdominal pain, nausea, vomiting, and anorexia 3 weeks after starting radiation therapy for prostate cancer. Physical examination shows abdominal tenderness. Sigmoidoscopy reveals hyperemia, edema, erosion, and ulceration of the intestinal mucosa. Stool and serum chemistries are normal. Radiation enteritis is suspected. Which of the following is most likely the primary mechanism responsible for this patient's intestinal changes?

○ A. Generation of reactive oxygen species
○ B. Increased activity of the ubiquitin-proteasome system
○ C. Inhibition of DNA polymerase
○ D. Inhibition of thymidylate synthesis
○ E. Prevention of microtubule assembly

Block Time Elapsed: 00:10:47

My Notebook
Flashcards
Feedback
Suspend
End Block

A 64-year-old man develops diarrhea, abdominal pain, nausea, vomiting, and anorexia 3 weeks after starting radiation therapy for prostate cancer. Physical examination shows abdominal tenderness. Sigmoidoscopy reveals hyperemia, edema, erosion, and ulceration of the intestinal mucosa. Stool and serum chemistries are normal. Radiation enteritis is suspected. Which of the following is most likely the primary mechanism responsible for this patient's intestinal changes?

✓ ○ A. Generation of reactive oxygen species (69%)
✗ ● B. Increased activity of the ubiquitin-proteasome system (10%)
○ C. Inhibition of DNA polymerase (8%)
○ D. Inhibition of thymidylate synthesis (7%)
○ E. Prevention of microtubule assembly (4%)

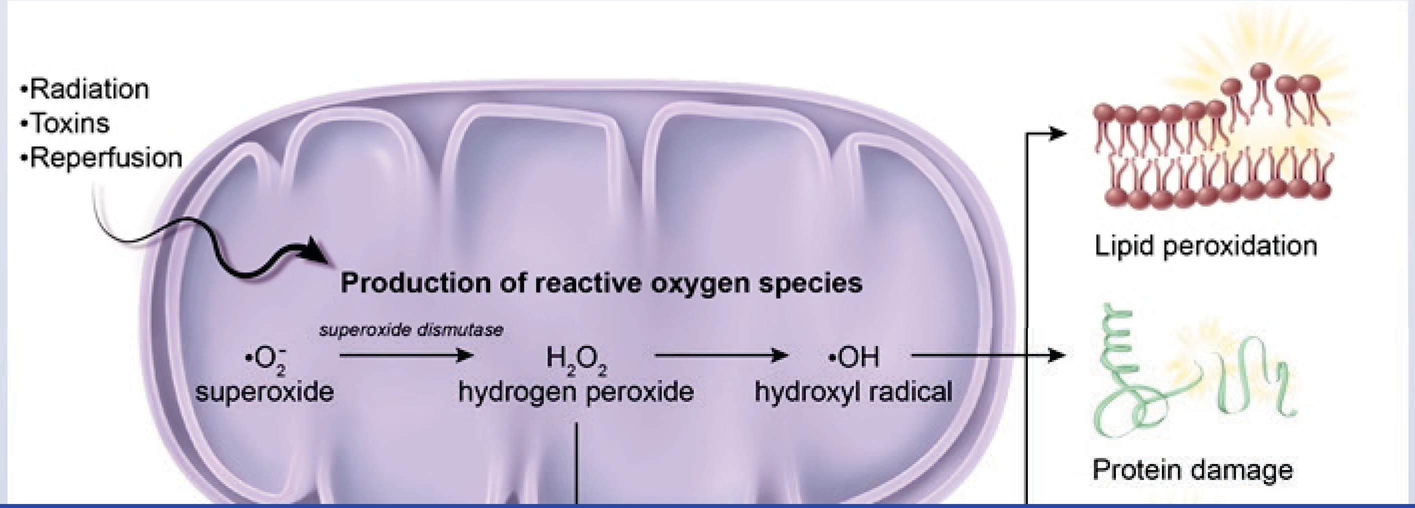
Incorrect
Correct answer
A

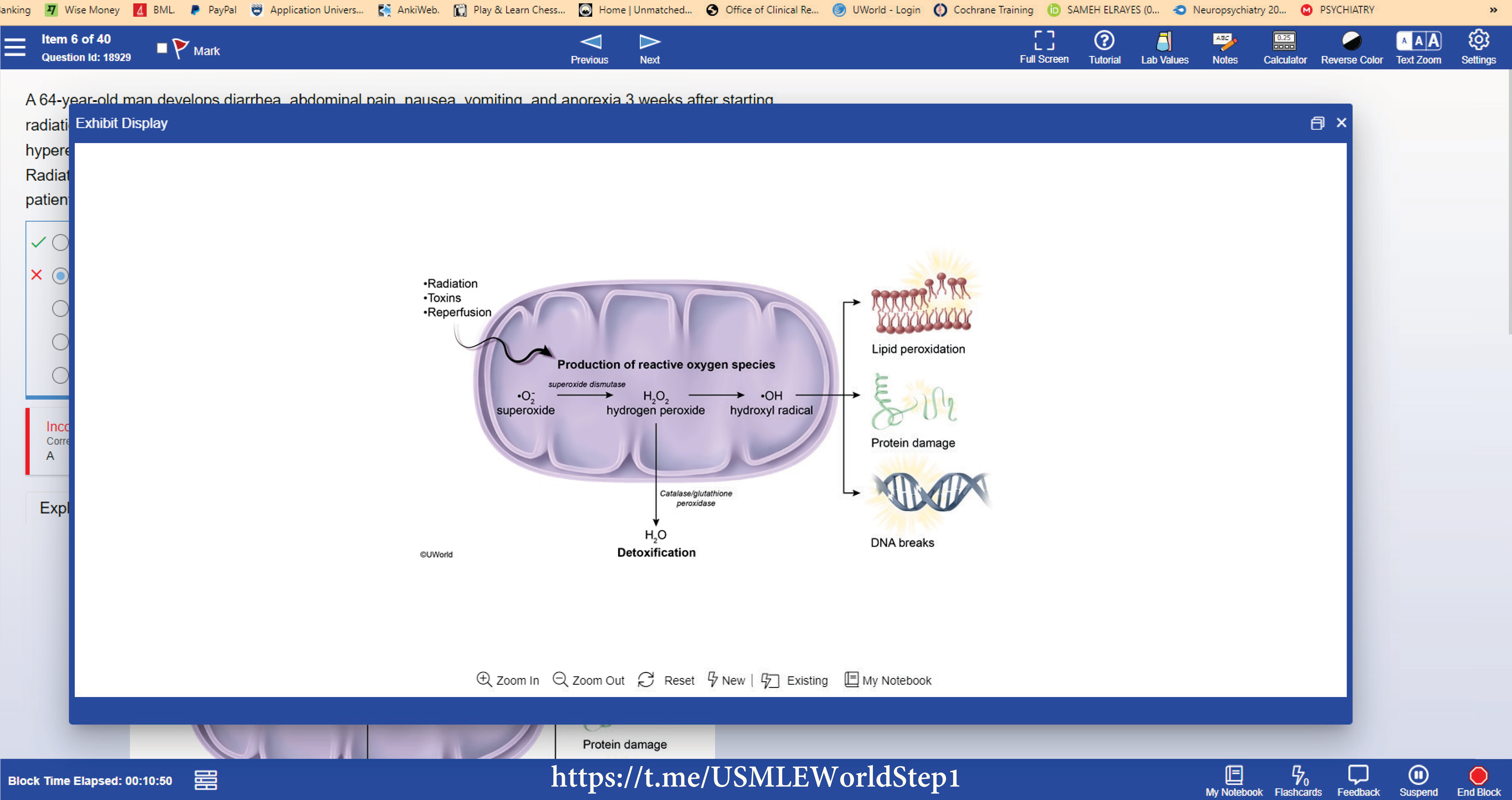
69%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation


•Radiation
•Toxins
•Reperfusion
Production of reactive oxygen species
superoxide dismutase
•O$_2^-$
superoxide
H$_2$O$_2$
hydrogen peroxide
•OH
hydroxyl radical
Lipid peroxidation
Protein damage


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Item 6 of 40
Question Id: 18929

A 64-year-old man develops diarrhea, abdominal pain, nausea, vomiting, and anorexia 3 weeks after starting
radiati
hypere
Radiat
patien

Inco
Corre
A

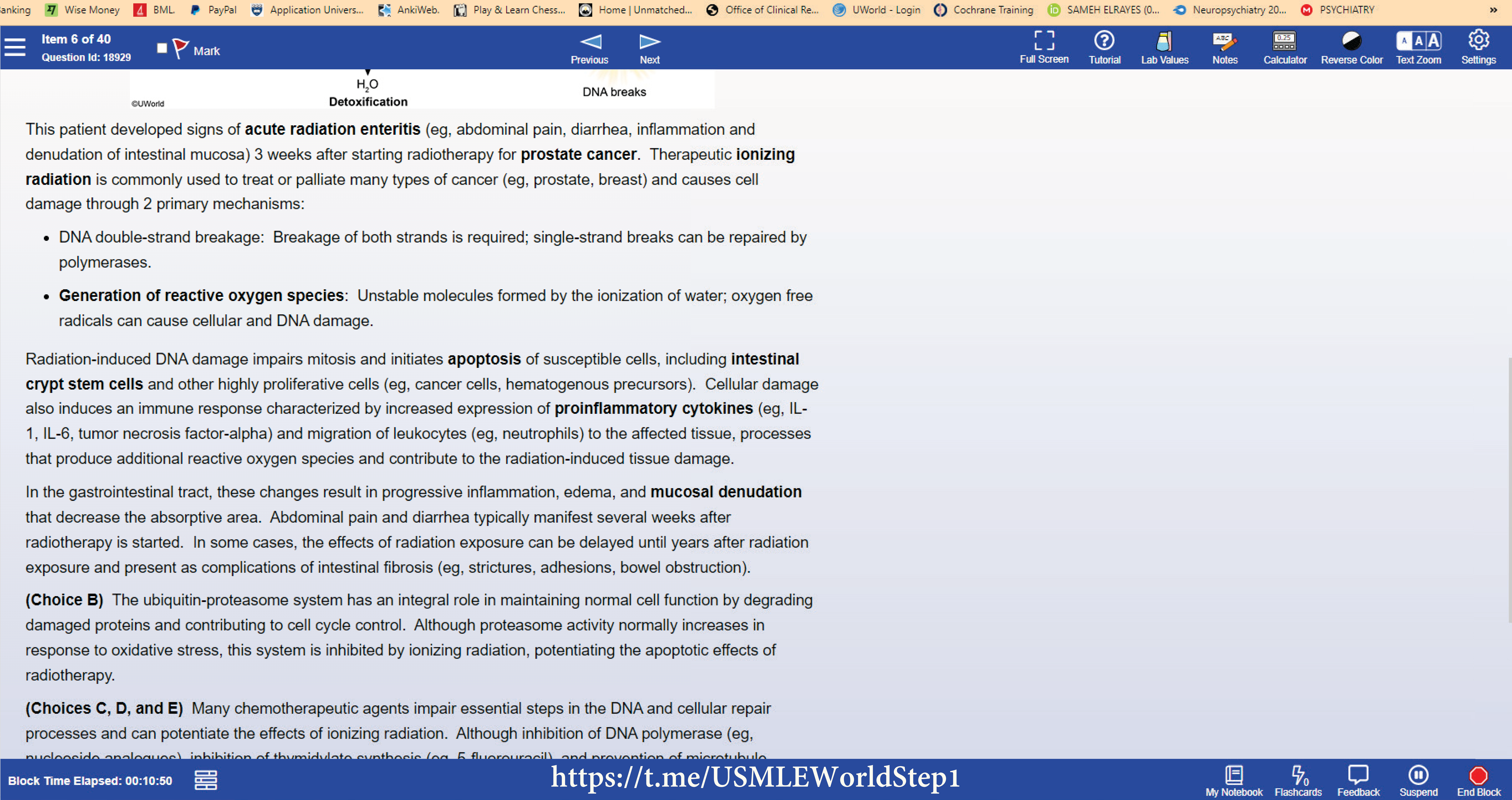
Expl

Exhibit Display

•Radiation
•Toxins
•Reperfusion
Production of reactive oxygen species
superoxide dismutase
$\cdot O_2^-$
superoxide
H_2O_2
hydrogen peroxide
•OH
hydroxyl radical
Catalase/glutathione peroxidase
H_2O
Detoxification
Lipid peroxidation
Protein damage
DNA breaks
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Protein damage

Block Time Elapsed: 00:10:50

My Notebook
Flashcards
Feedback
Suspend
End Block



This patient developed signs of **acute radiation enteritis** (eg, abdominal pain, diarrhea, inflammation and denudation of intestinal mucosa) 3 weeks after starting radiotherapy for **prostate cancer**. Therapeutic **ionizing radiation** is commonly used to treat or palliate many types of cancer (eg, prostate, breast) and causes cell damage through 2 primary mechanisms:

- DNA double-strand breakage: Breakage of both strands is required; single-strand breaks can be repaired by polymerases.
- **Generation of reactive oxygen species**: Unstable molecules formed by the ionization of water; oxygen free radicals can cause cellular and DNA damage.

Radiation-induced DNA damage impairs mitosis and initiates **apoptosis** of susceptible cells, including **intestinal crypt stem cells** and other highly proliferative cells (eg, cancer cells, hematogenous precursors). Cellular damage also induces an immune response characterized by increased expression of **proinflammatory cytokines** (eg, IL-1, IL-6, tumor necrosis factor-alpha) and migration of leukocytes (eg, neutrophils) to the affected tissue, processes that produce additional reactive oxygen species and contribute to the radiation-induced tissue damage.

In the gastrointestinal tract, these changes result in progressive inflammation, edema, and **mucosal denudation** that decrease the absorptive area. Abdominal pain and diarrhea typically manifest several weeks after radiotherapy is started. In some cases, the effects of radiation exposure can be delayed until years after radiation exposure and present as complications of intestinal fibrosis (eg, strictures, adhesions, bowel obstruction).

(Choice B) The ubiquitin-proteasome system has an integral role in maintaining normal cell function by degrading damaged proteins and contributing to cell cycle control. Although proteasome activity normally increases in response to oxidative stress, this system is inhibited by ionizing radiation, potentiating the apoptotic effects of radiotherapy.

(Choices C, D, and E) Many chemotherapeutic agents impair essential steps in the DNA and cellular repair processes and can potentiate the effects of ionizing radiation. Although inhibition of DNA polymerase (eg, nucleoside analogues), inhibition of thymidylate synthesis (eg, 5-fluorouracil), and prevention of microtubule radicals can cause cellular and DNA damage.

Radiation-induced DNA damage impairs mitosis and initiates **apoptosis** of susceptible cells, including **intestinal crypt stem cells** and other highly proliferative cells (eg, cancer cells, hematogenous precursors). Cellular damage also induces an immune response characterized by increased expression of **proinflammatory cytokines** (eg, IL-1, IL-6, tumor necrosis factor-alpha) and migration of leukocytes (eg, neutrophils) to the affected tissue, processes that produce additional reactive oxygen species and contribute to the radiation-induced tissue damage.

In the gastrointestinal tract, these changes result in progressive inflammation, edema, and **mucosal denudation** that decrease the absorptive area. Abdominal pain and diarrhea typically manifest several weeks after radiotherapy is started. In some cases, the effects of radiation exposure can be delayed until years after radiation exposure and present as complications of intestinal fibrosis (eg, strictures, adhesions, bowel obstruction).

(Choice B) The ubiquitin-proteasome system has an integral role in maintaining normal cell function by degrading damaged proteins and contributing to cell cycle control. Although proteasome activity normally increases in response to oxidative stress, this system is inhibited by ionizing radiation, potentiating the apoptotic effects of radiotherapy.

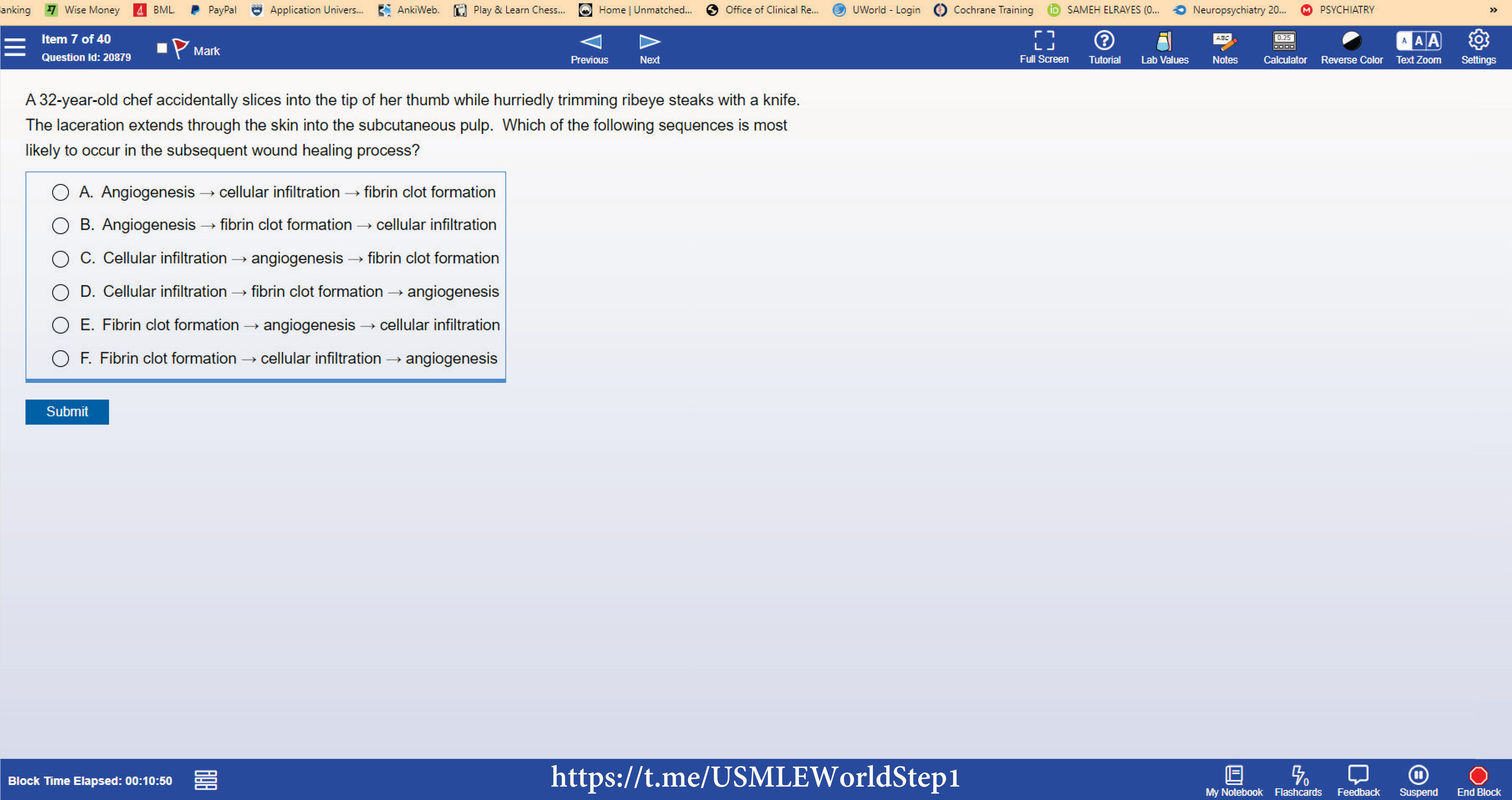
(Choices C, D, and E) Many chemotherapeutic agents impair essential steps in the DNA and cellular repair processes and can potentiate the effects of ionizing radiation. Although inhibition of DNA polymerase (eg, nucleoside analogues), inhibition of thymidylate synthesis (eg, 5-fluorouracil), and prevention of microtubule assembly (eg, vinblastine) would contribute to the cytotoxic effects of radiation, radiation-induced tissue damage occurs primarily through the generation of free radicals.

Educational objective:

Ionizing radiation causes cellular and DNA damage primarily through generation of reactive oxygen species, which can trigger progressive inflammation and tissue damage. In the gastrointestinal tract, the acute effects of radiation exposure typically occur several weeks after radiotherapy is initiated and manifest as abdominal pain and diarrhea due to mucosal denudation, inflammation, and edema.

References

- Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 7 of 40
Question Id: 20879
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 32-year-old chef accidentally slices into the tip of her thumb while hurriedly trimming ribeye steaks with a knife. The laceration extends through the skin into the subcutaneous pulp. Which of the following sequences is most likely to occur in the subsequent wound healing process?

○ A. Angiogenesis → cellular infiltration → fibrin clot formation

○ B. Angiogenesis → fibrin clot formation → cellular infiltration

○ C. Cellular infiltration → angiogenesis → fibrin clot formation

○ D. Cellular infiltration → fibrin clot formation → angiogenesis

○ E. Fibrin clot formation → angiogenesis → cellular infiltration

○ F. Fibrin clot formation → cellular infiltration → angiogenesis

Submit
Block Time Elapsed: 00:10:50
My Notebook
Flashcards
Feedback
Suspend
End Block

A 32-year-old chef accidentally slices into the tip of her thumb while hurriedly trimming ribeye steaks with a knife. The laceration extends through the skin into the subcutaneous pulp. Which of the following sequences is most likely to occur in the subsequent wound healing process?

○ A. Angiogenesis → cellular infiltration → fibrin clot formation (1%)
○ B. Angiogenesis → fibrin clot formation → cellular infiltration (0%)
✗ ● C. Cellular infiltration → angiogenesis → fibrin clot formation (4%)
○ D. Cellular infiltration → fibrin clot formation → angiogenesis (21%)
○ E. Fibrin clot formation → angiogenesis → cellular infiltration (3%)
✓ ○ F. Fibrin clot formation → cellular infiltration → angiogenesis (68%)

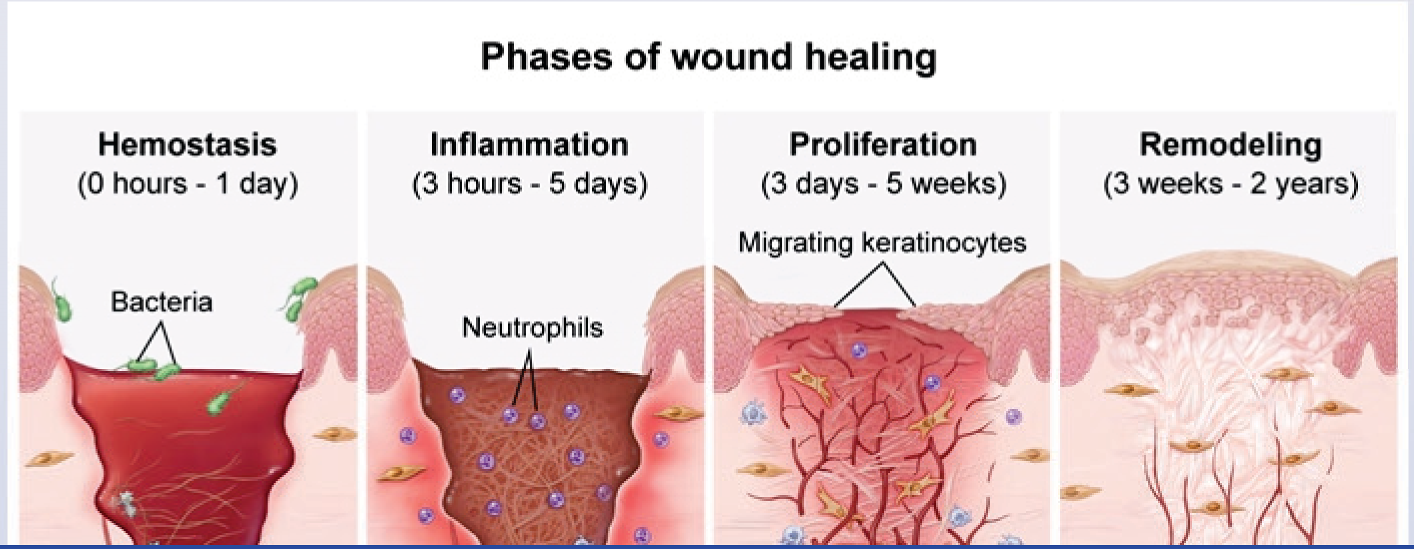
Incorrect
Correct answer
F

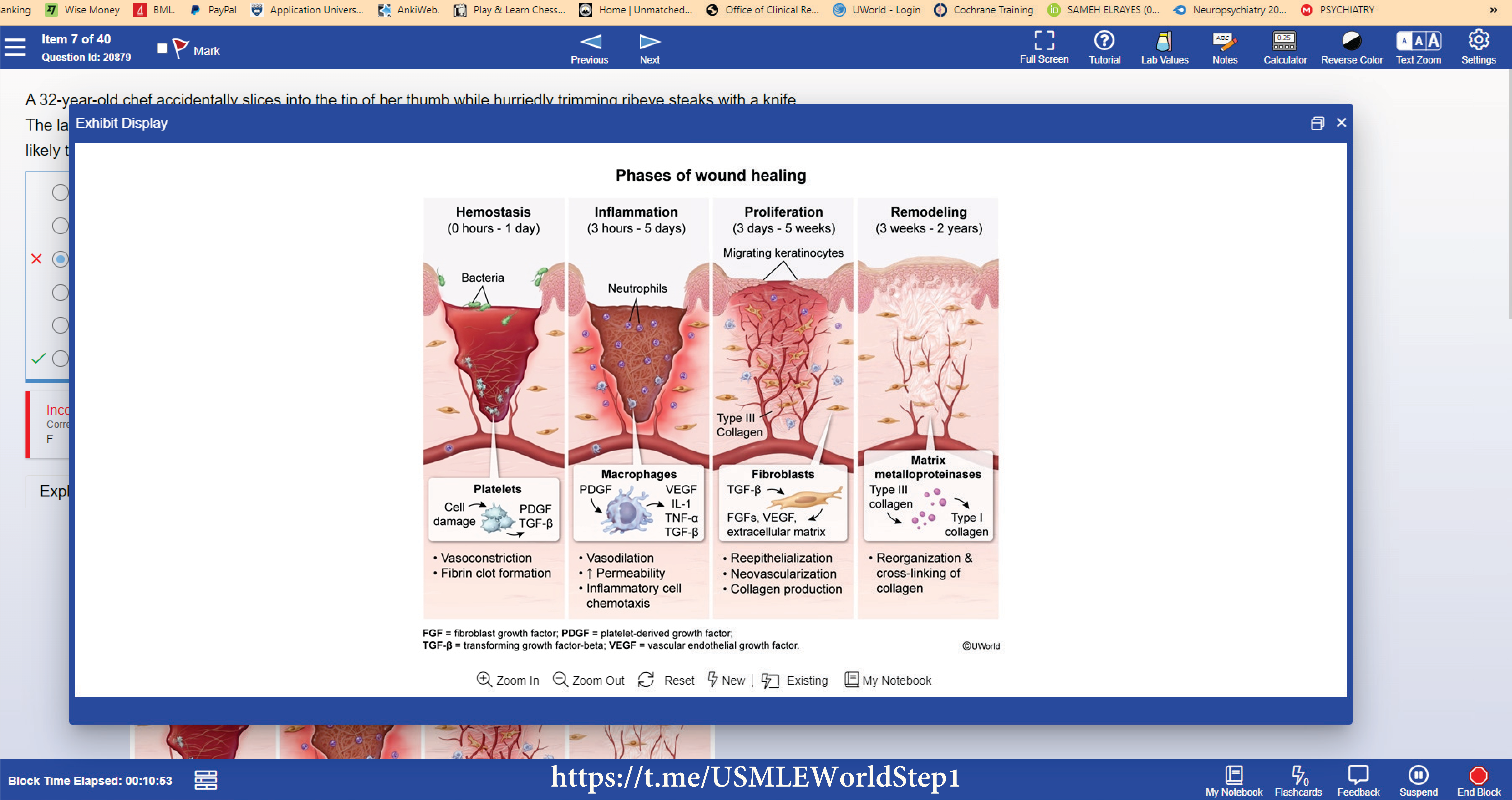
68%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation


Phases of wound healing
Hemostasis
(0 hours - 1 day)
Inflammation
(3 hours - 5 days)
Proliferation
(3 days - 5 weeks)
Remodeling
(3 weeks - 2 years)
Bacteria
Neutrophils
Migrating keratinocytes


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 7 of 40
Question Id: 20879
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 32-year-old chef accidentally slices into the tip of her thumb while hurriedly trimming ribeye steaks with a knife.

The la

likely t

○

○

✗ ●

○

○

✓ ○

Inco

Corre

F

Expl

Exhibit Display

Phases of wound healing

Hemostasis
(0 hours - 1 day)
Bacteria
Platelets
Cell damage
PDGF
TGF-β
• Vasoconstriction
• Fibrin clot formation
Inflammation
(3 hours - 5 days)
Neutrophils
Macrophages
PDGF
VEGF
IL-1
TNF-α
TGF-β
• Vasodilation
• ↑ Permeability
• Inflammatory cell chemotaxis
Proliferation
(3 days - 5 weeks)
Migrating keratinocytes
Type III Collagen
Fibroblasts
TGF-β
FGFs, VEGF, extracellular matrix
• Reepithelialization
• Neovascularization
• Collagen production
Remodeling
(3 weeks - 2 years)
Matrix metalloproteinases
Type III collagen
Type I collagen
• Reorganization & cross-linking of collagen

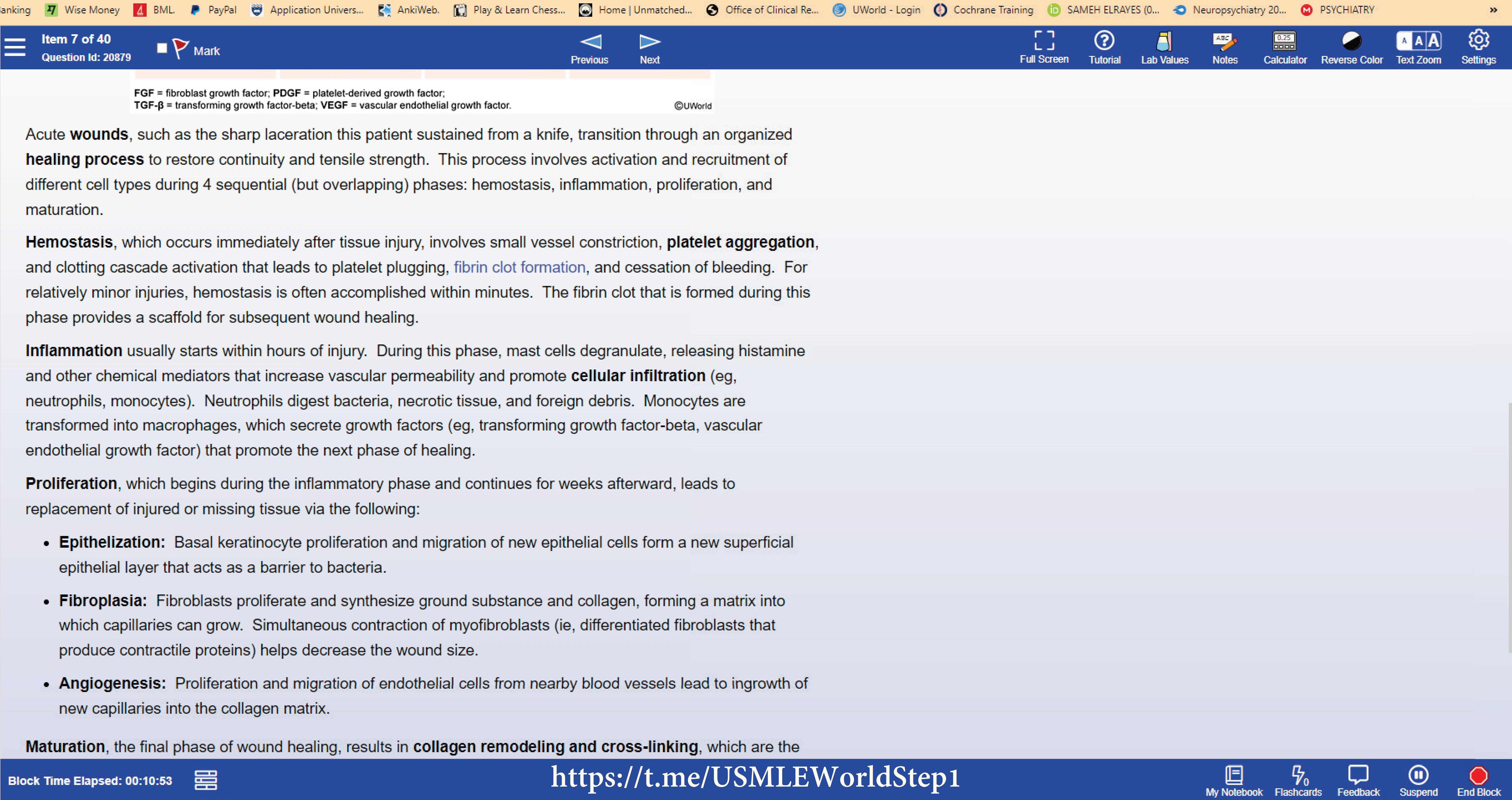
FGF = fibroblast growth factor; **PDGF** = platelet-derived growth factor;
TGF-β = transforming growth factor-beta; **VEGF** = vascular endothelial growth factor.

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:10:53

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 7 of 40
Question Id: 20879
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:10:53
My Notebook
Flashcards
Feedback
Suspend
End Block

FGF = fibroblast growth factor; **PDGF** = platelet-derived growth factor;
TGF-β = transforming growth factor-beta; **VEGF** = vascular endothelial growth factor.

©UWorld

Acute **wounds**, such as the sharp laceration this patient sustained from a knife, transition through an organized **healing process** to restore continuity and tensile strength. This process involves activation and recruitment of different cell types during 4 sequential (but overlapping) phases: hemostasis, inflammation, proliferation, and maturation.

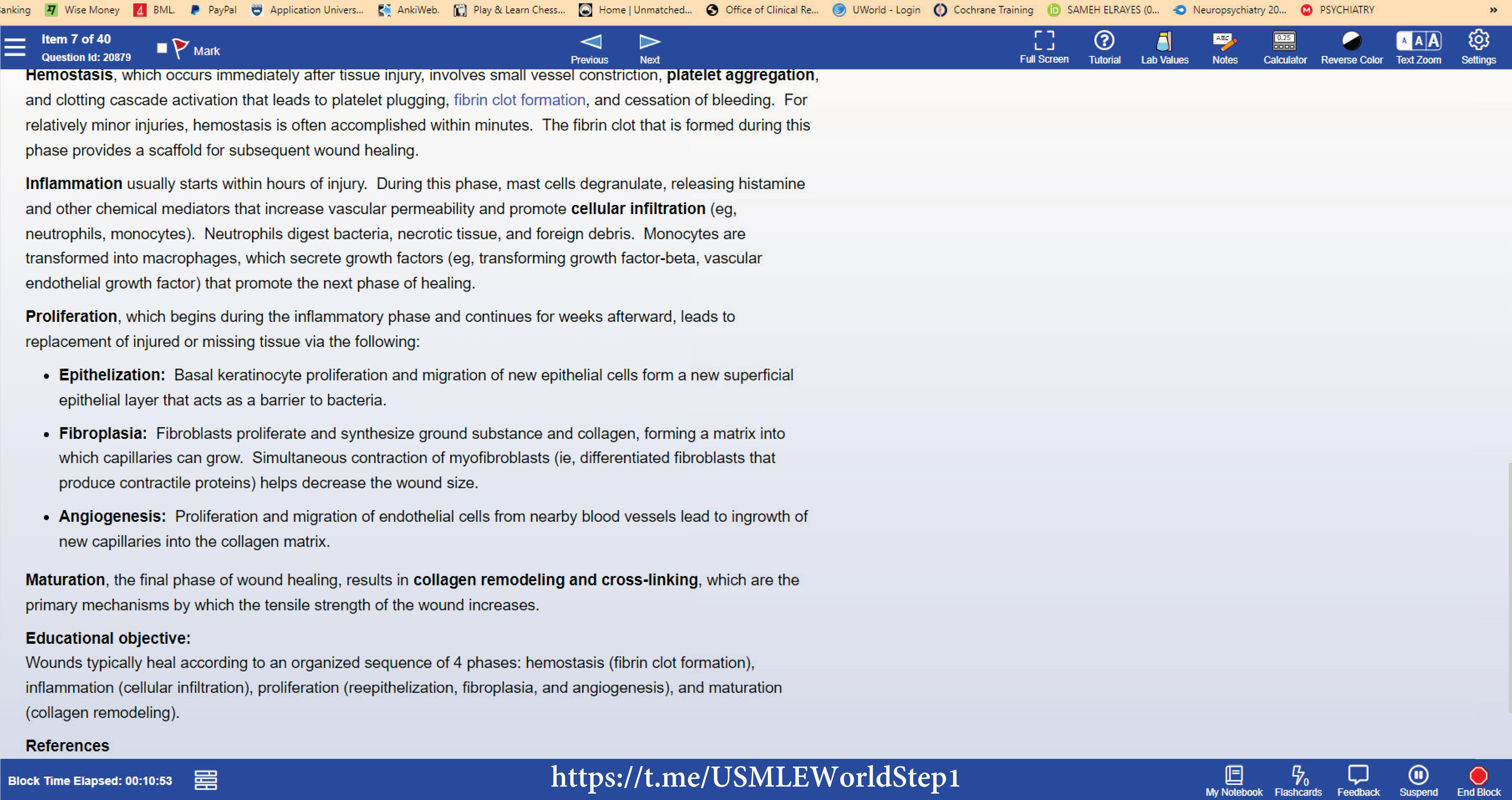
Hemostasis, which occurs immediately after tissue injury, involves small vessel constriction, **platelet aggregation**, and clotting cascade activation that leads to platelet plugging, fibrin clot formation, and cessation of bleeding. For relatively minor injuries, hemostasis is often accomplished within minutes. The fibrin clot that is formed during this phase provides a scaffold for subsequent wound healing.

Inflammation usually starts within hours of injury. During this phase, mast cells degranulate, releasing histamine and other chemical mediators that increase vascular permeability and promote **cellular infiltration** (eg, neutrophils, monocytes). Neutrophils digest bacteria, necrotic tissue, and foreign debris. Monocytes are transformed into macrophages, which secrete growth factors (eg, transforming growth factor-beta, vascular endothelial growth factor) that promote the next phase of healing.

Proliferation, which begins during the inflammatory phase and continues for weeks afterward, leads to replacement of injured or missing tissue via the following:

- **Epithelization:** Basal keratinocyte proliferation and migration of new epithelial cells form a new superficial epithelial layer that acts as a barrier to bacteria.
- **Fibroplasia:** Fibroblasts proliferate and synthesize ground substance and collagen, forming a matrix into which capillaries can grow. Simultaneous contraction of myofibroblasts (ie, differentiated fibroblasts that produce contractile proteins) helps decrease the wound size.
- **Angiogenesis:** Proliferation and migration of endothelial cells from nearby blood vessels lead to ingrowth of new capillaries into the collagen matrix.

Maturation, the final phase of wound healing, results in **collagen remodeling and cross-linking**, which are the


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 7 of 40
Question Id: 20879
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Hemostasis, which occurs immediately after tissue injury, involves small vessel constriction, **platelet aggregation**, and clotting cascade activation that leads to platelet plugging, fibrin clot formation, and cessation of bleeding. For relatively minor injuries, hemostasis is often accomplished within minutes. The fibrin clot that is formed during this phase provides a scaffold for subsequent wound healing.

Inflammation usually starts within hours of injury. During this phase, mast cells degranulate, releasing histamine and other chemical mediators that increase vascular permeability and promote **cellular infiltration** (eg, neutrophils, monocytes). Neutrophils digest bacteria, necrotic tissue, and foreign debris. Monocytes are transformed into macrophages, which secrete growth factors (eg, transforming growth factor-beta, vascular endothelial growth factor) that promote the next phase of healing.

Proliferation, which begins during the inflammatory phase and continues for weeks afterward, leads to replacement of injured or missing tissue via the following:

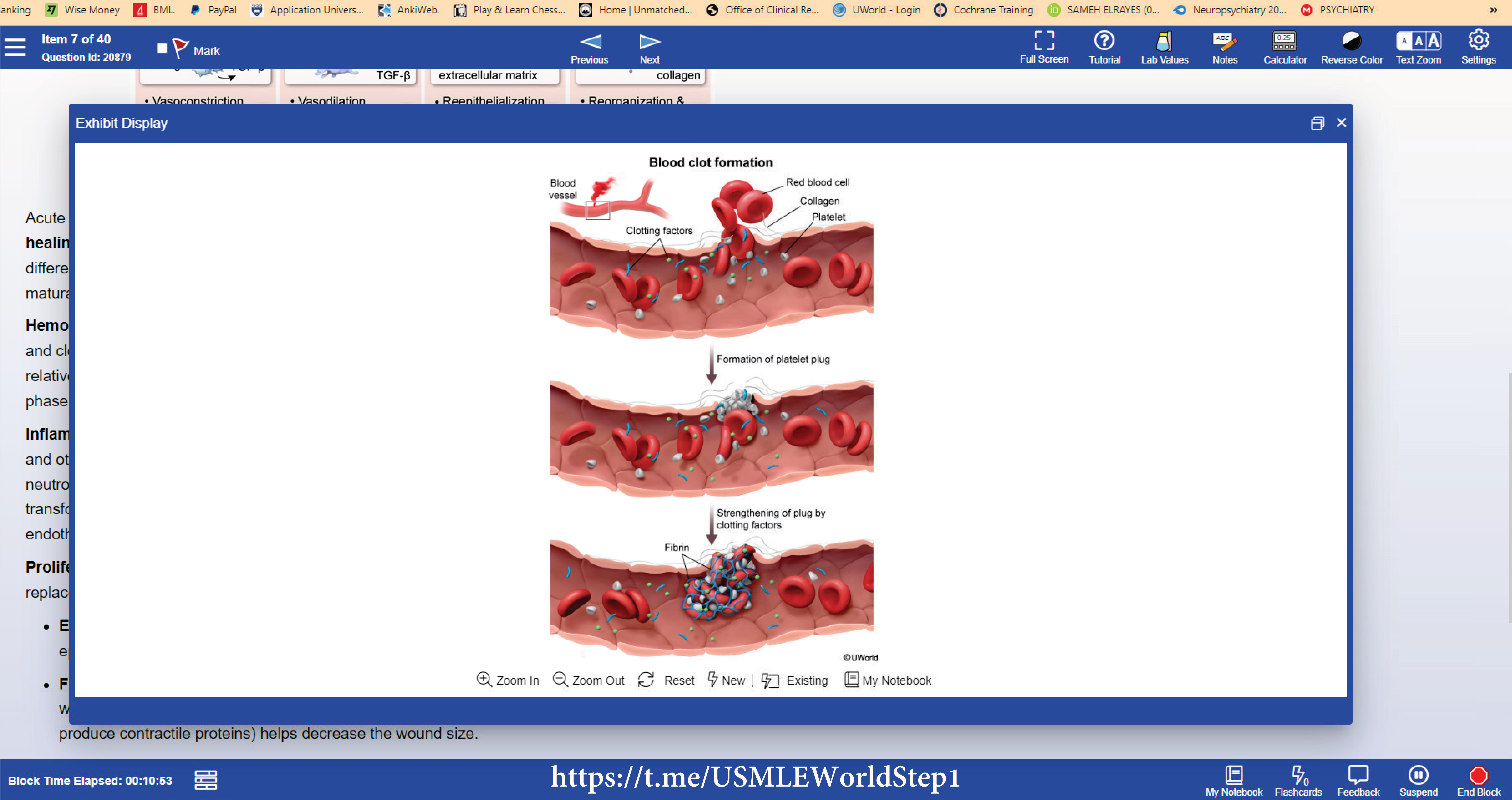
- **Epithelization:** Basal keratinocyte proliferation and migration of new epithelial cells form a new superficial epithelial layer that acts as a barrier to bacteria.
- **Fibroplasia:** Fibroblasts proliferate and synthesize ground substance and collagen, forming a matrix into which capillaries can grow. Simultaneous contraction of myofibroblasts (ie, differentiated fibroblasts that produce contractile proteins) helps decrease the wound size.
- **Angiogenesis:** Proliferation and migration of endothelial cells from nearby blood vessels lead to ingrowth of new capillaries into the collagen matrix.

Maturation, the final phase of wound healing, results in **collagen remodeling and cross-linking**, which are the primary mechanisms by which the tensile strength of the wound increases.

Educational objective:
Wounds typically heal according to an organized sequence of 4 phases: hemostasis (fibrin clot formation), inflammation (cellular infiltration), proliferation (reepithelization, fibroplasia, and angiogenesis), and maturation (collagen remodeling).

References

Block Time Elapsed: 00:10:53
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 7 of 40
Question Id: 20879
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
TGF-β
extracellular matrix
collagen
• Vasoconstriction
• Vasodilation
• Reepithelialization
• Reorganization &
Exhibit Display

Blood clot formation

Blood vessel
Red blood cell
Collagen
Platelet
Clotting factors
Formation of platelet plug
Strengthening of plug by clotting factors
Fibrin
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Acute
healin
differe
matura

Hemo
and cl
relativ
phase

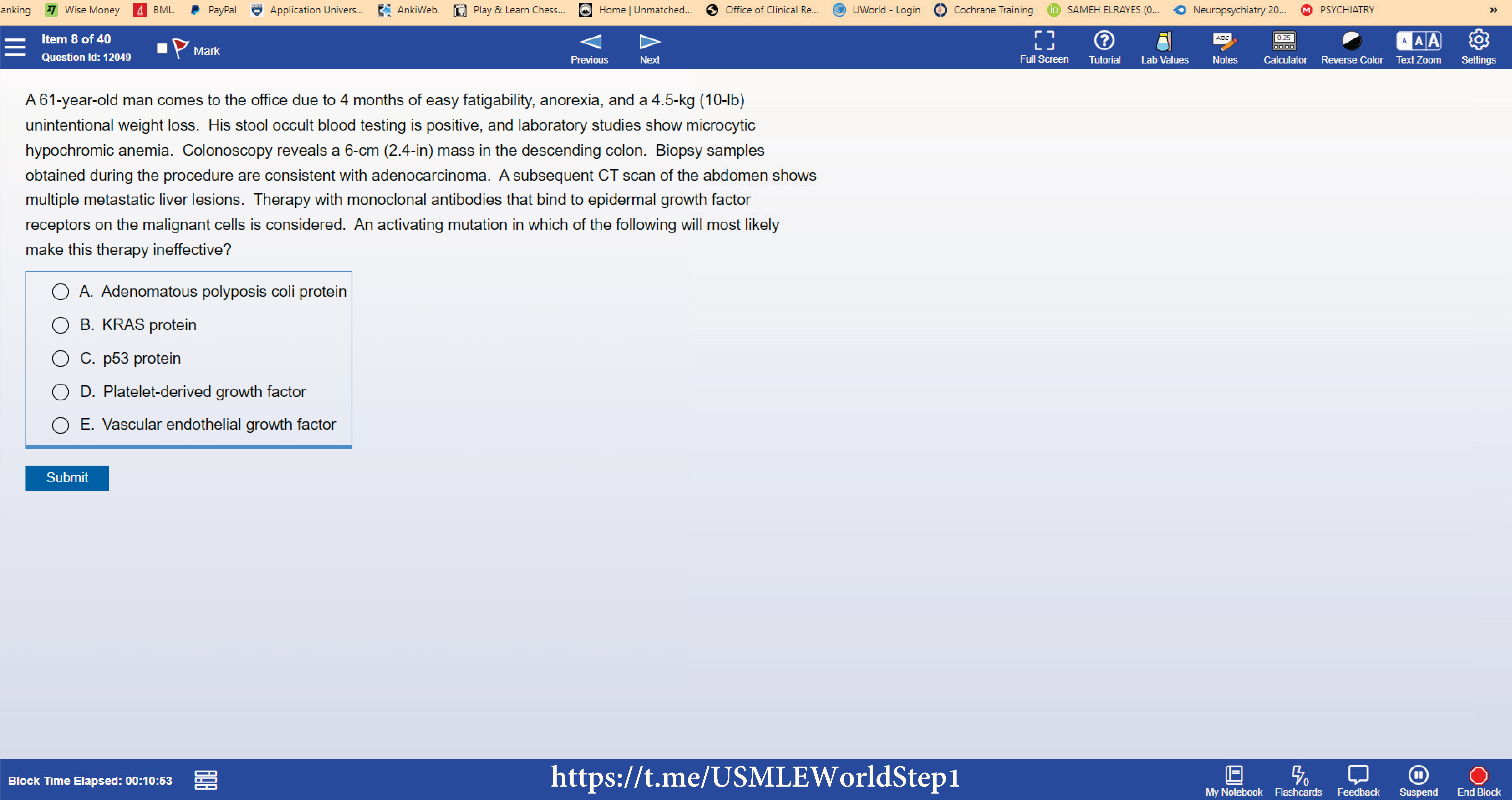
Inflam
and ot
neutro
transfo
endoth

Prolif
replac

- **E**
  e
- **F**
  w

produce contractile proteins) helps decrease the wound size.

Block Time Elapsed: 00:10:53
My Notebook
Flashcards
Feedback
Suspend
End Block

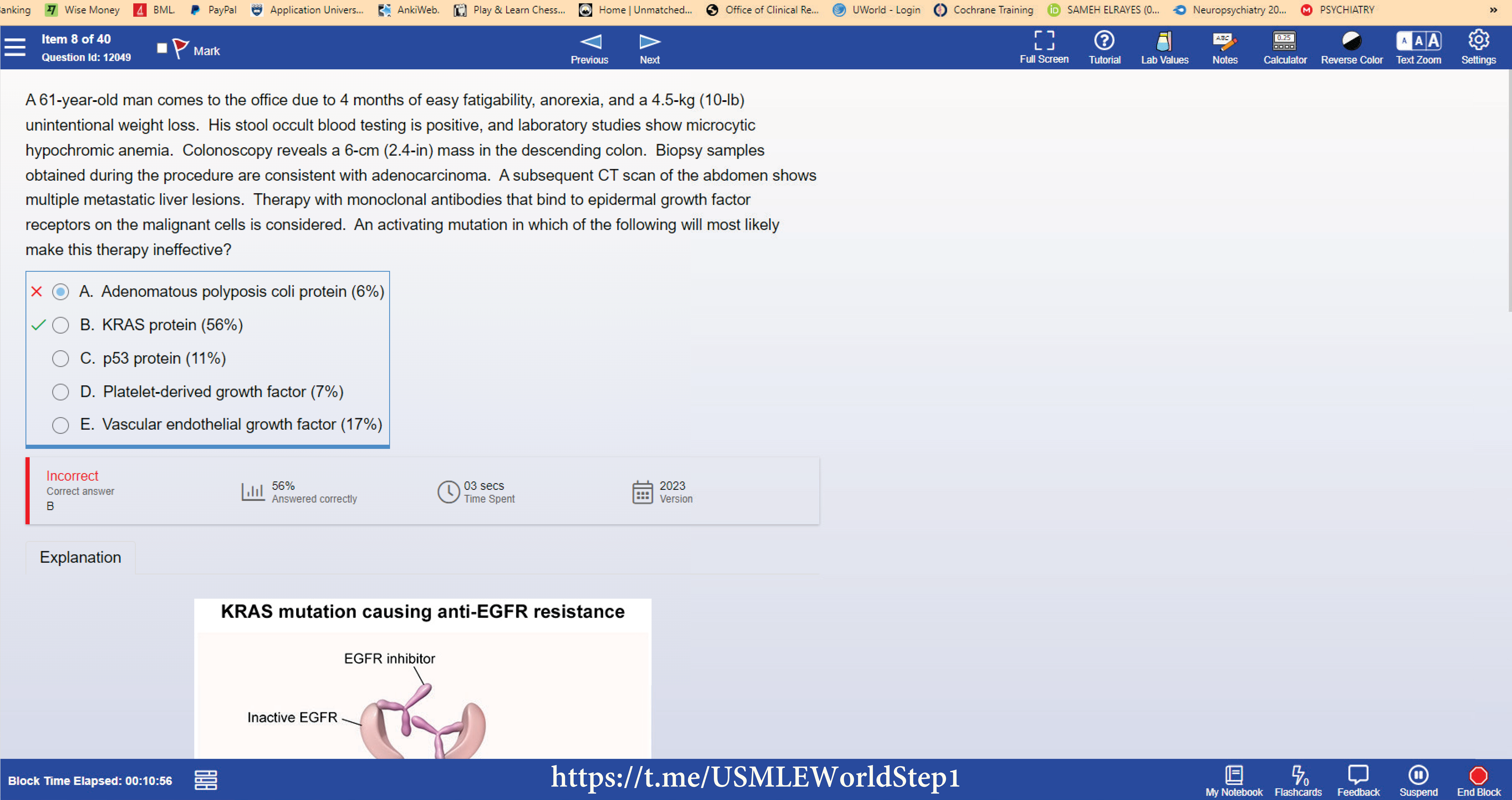

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 8 of 40
Question Id: 12049
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 61-year-old man comes to the office due to 4 months of easy fatigability, anorexia, and a 4.5-kg (10-lb) unintentional weight loss. His stool occult blood testing is positive, and laboratory studies show microcytic hypochromic anemia. Colonoscopy reveals a 6-cm (2.4-in) mass in the descending colon. Biopsy samples obtained during the procedure are consistent with adenocarcinoma. A subsequent CT scan of the abdomen shows multiple metastatic liver lesions. Therapy with monoclonal antibodies that bind to epidermal growth factor receptors on the malignant cells is considered. An activating mutation in which of the following will most likely make this therapy ineffective?

○ A. Adenomatous polyposis coli protein
○ B. KRAS protein
○ C. p53 protein
○ D. Platelet-derived growth factor
○ E. Vascular endothelial growth factor

Submit
Block Time Elapsed: 00:10:53

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 8 of 40
Question Id: 12049
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 61-year-old man comes to the office due to 4 months of easy fatigability, anorexia, and a 4.5-kg (10-lb) unintentional weight loss. His stool occult blood testing is positive, and laboratory studies show microcytic hypochromic anemia. Colonoscopy reveals a 6-cm (2.4-in) mass in the descending colon. Biopsy samples obtained during the procedure are consistent with adenocarcinoma. A subsequent CT scan of the abdomen shows multiple metastatic liver lesions. Therapy with monoclonal antibodies that bind to epidermal growth factor receptors on the malignant cells is considered. An activating mutation in which of the following will most likely make this therapy ineffective?

- ✗ ● A. Adenomatous polyposis coli protein (6%)
- ✓ ○ B. KRAS protein (56%)
- ○ C. p53 protein (11%)
- ○ D. Platelet-derived growth factor (7%)
- ○ E. Vascular endothelial growth factor (17%)

Incorrect
Correct answer
B

56%
Answered correctly

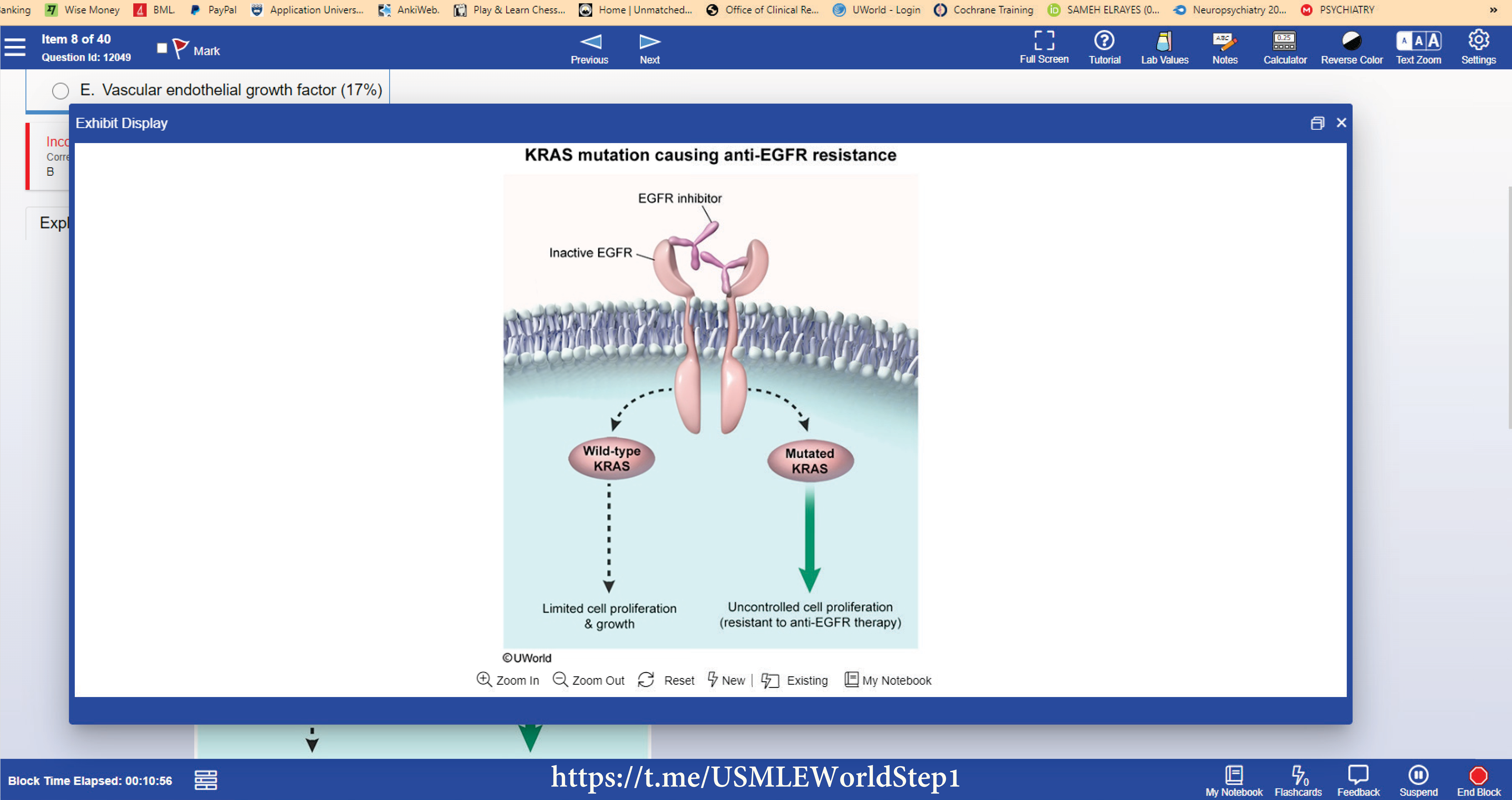
03 secs
Time Spent

2023
Version

Explanation

KRAS mutation causing anti-EGFR resistance

EGFR inhibitor
Inactive EGFR
Block Time Elapsed: 00:10:56
https://t.me/USMLEWorldStep1
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 8 of 40
Question Id: 12049
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

○ E. Vascular endothelial growth factor (17%)

Inco
Corre
B
Expl
Exhibit Display

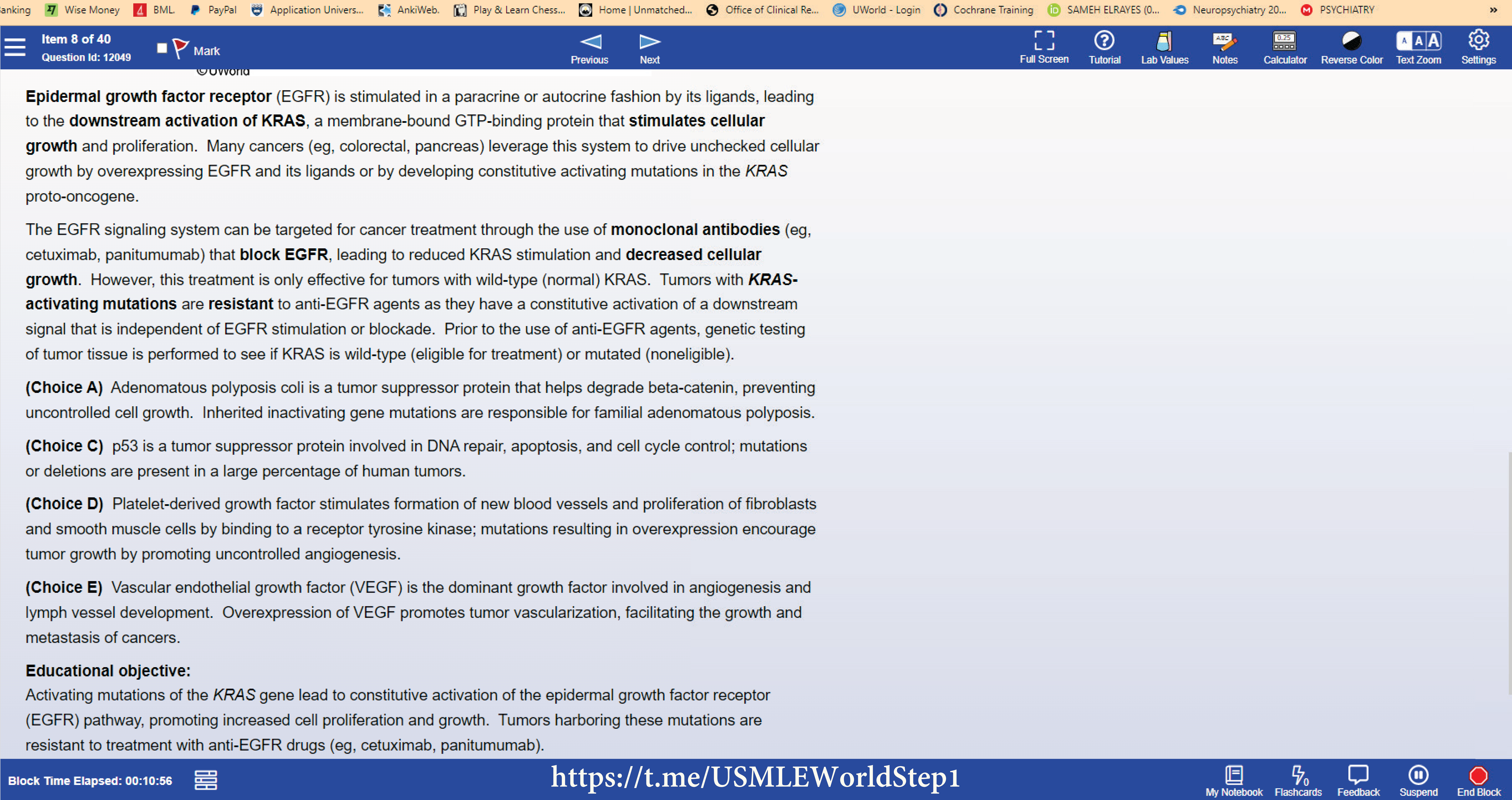
KRAS mutation causing anti-EGFR resistance

EGFR inhibitor
Inactive EGFR
Wild-type KRAS
Mutated KRAS
Limited cell proliferation & growth
Uncontrolled cell proliferation (resistant to anti-EGFR therapy)

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:10:56
My Notebook
Flashcards
Feedback
Suspend
End Block

https://t.me/USMLEWorldStep1


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 8 of 40
Question Id: 12049
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld

Epidermal growth factor receptor (EGFR) is stimulated in a paracrine or autocrine fashion by its ligands, leading to the **downstream activation of KRAS**, a membrane-bound GTP-binding protein that **stimulates cellular growth** and proliferation. Many cancers (eg, colorectal, pancreas) leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations in the *KRAS* proto-oncogene.

The EGFR signaling system can be targeted for cancer treatment through the use of **monoclonal antibodies** (eg, cetuximab, panitumumab) that **block EGFR**, leading to reduced KRAS stimulation and **decreased cellular growth**. However, this treatment is only effective for tumors with wild-type (normal) KRAS. Tumors with ***KRAS*-activating mutations** are **resistant** to anti-EGFR agents as they have a constitutive activation of a downstream signal that is independent of EGFR stimulation or blockade. Prior to the use of anti-EGFR agents, genetic testing of tumor tissue is performed to see if KRAS is wild-type (eligible for treatment) or mutated (noneligible).

(Choice A) Adenomatous polyposis coli is a tumor suppressor protein that helps degrade beta-catenin, preventing uncontrolled cell growth. Inherited inactivating gene mutations are responsible for familial adenomatous polyposis.

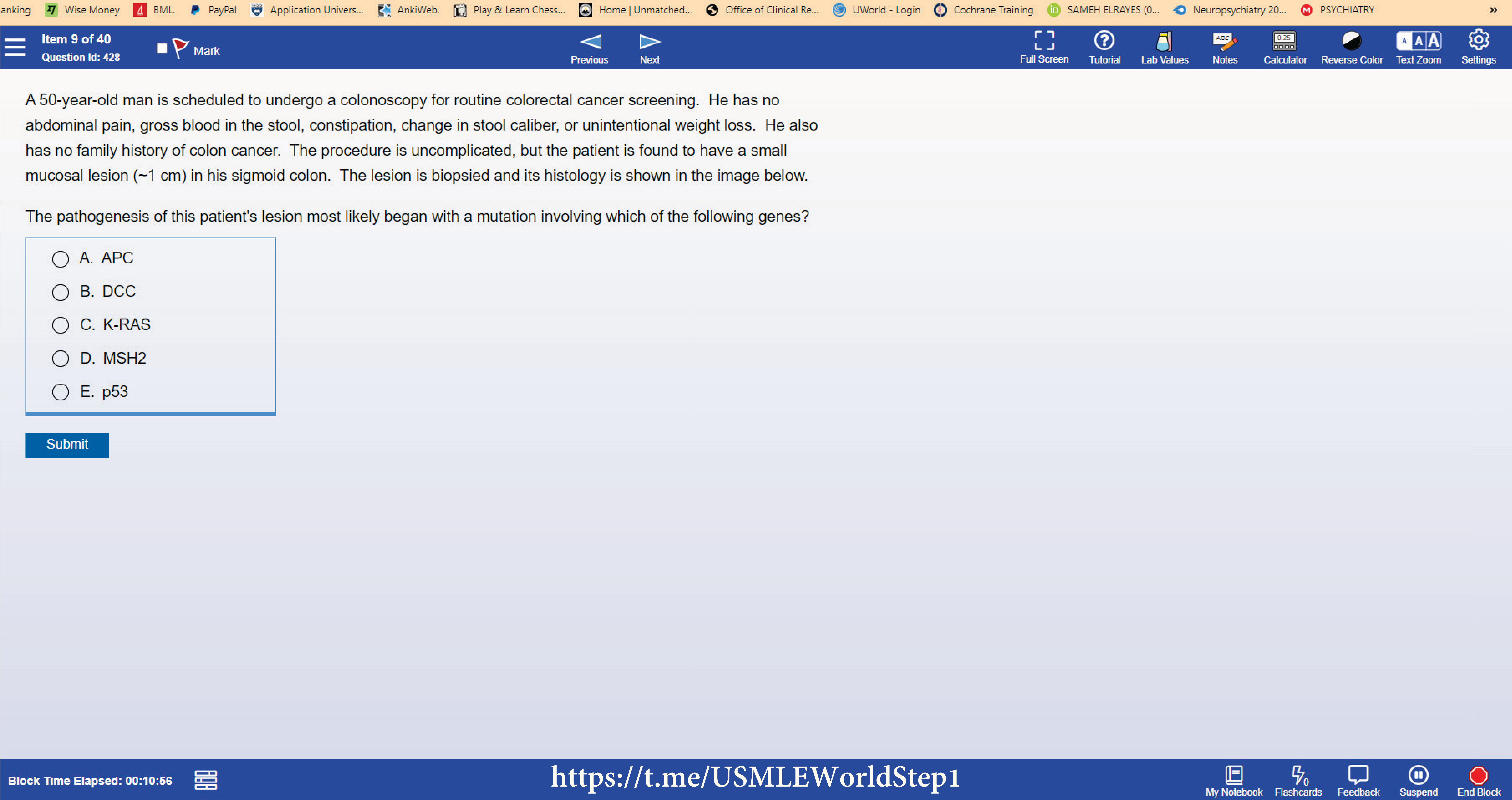
(Choice C) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control; mutations or deletions are present in a large percentage of human tumors.

(Choice D) Platelet-derived growth factor stimulates formation of new blood vessels and proliferation of fibroblasts and smooth muscle cells by binding to a receptor tyrosine kinase; mutations resulting in overexpression encourage tumor growth by promoting uncontrolled angiogenesis.

(Choice E) Vascular endothelial growth factor (VEGF) is the dominant growth factor involved in angiogenesis and lymph vessel development. Overexpression of VEGF promotes tumor vascularization, facilitating the growth and metastasis of cancers.

Educational objective:
Activating mutations of the *KRAS* gene lead to constitutive activation of the epidermal growth factor receptor (EGFR) pathway, promoting increased cell proliferation and growth. Tumors harboring these mutations are resistant to treatment with anti-EGFR drugs (eg, cetuximab, panitumumab).

Block Time Elapsed: 00:10:56
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 9 of 40
Question Id: 428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:10:56
My Notebook
Flashcards
Feedback
Suspend
End Block

A 50-year-old man is scheduled to undergo a colonoscopy for routine colorectal cancer screening. He has no abdominal pain, gross blood in the stool, constipation, change in stool caliber, or unintentional weight loss. He also has no family history of colon cancer. The procedure is uncomplicated, but the patient is found to have a small mucosal lesion (~1 cm) in his sigmoid colon. The lesion is biopsied and its histology is shown in the image below.

The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

○ A. APC
○ B. DCC
○ C. K-RAS
○ D. MSH2
○ E. p53

Submit

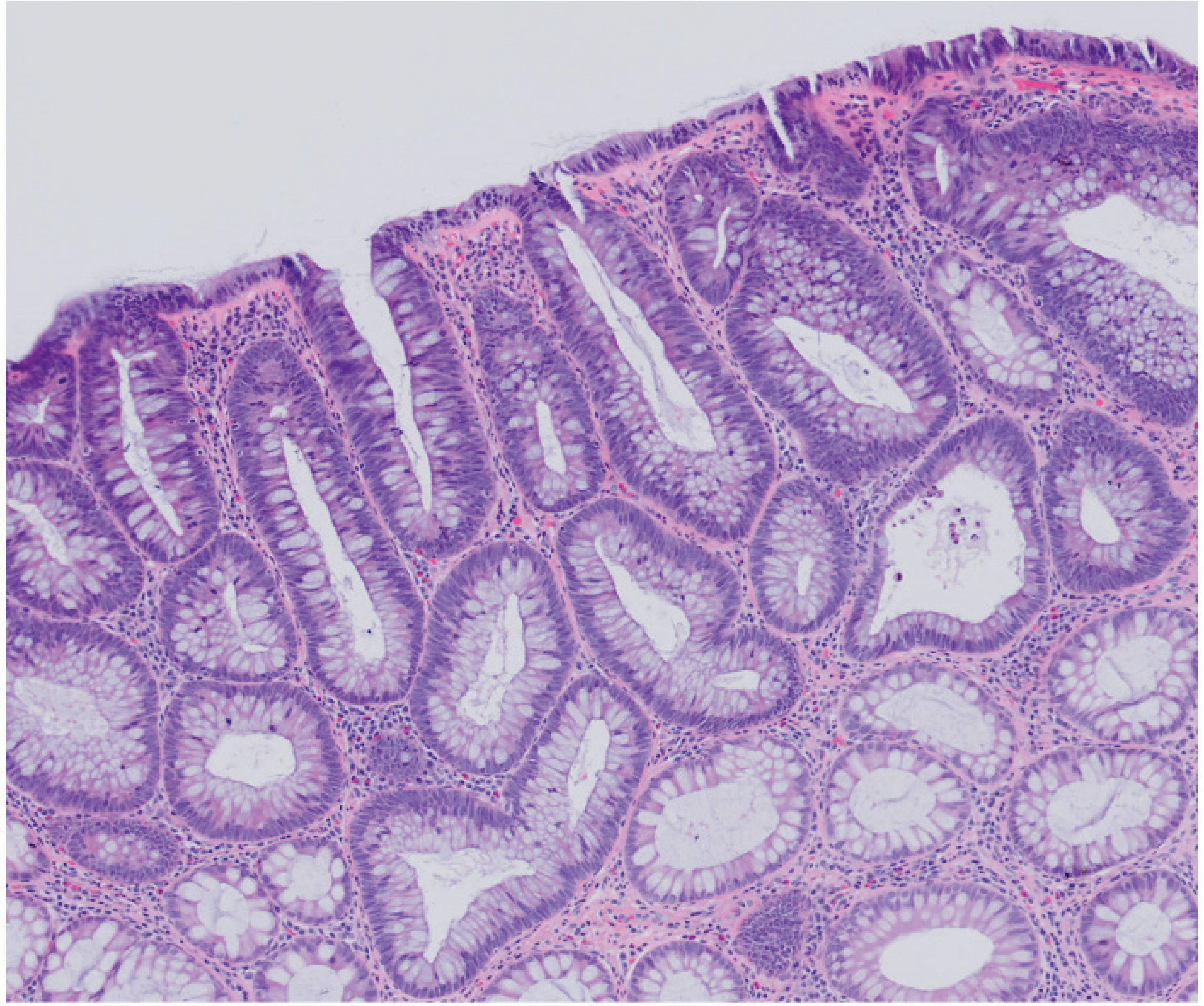
A 50-year-old man is scheduled to undergo a colonoscopy for routine colorectal cancer screening. He has no

abdom

has no

mucos

Exhibit Display

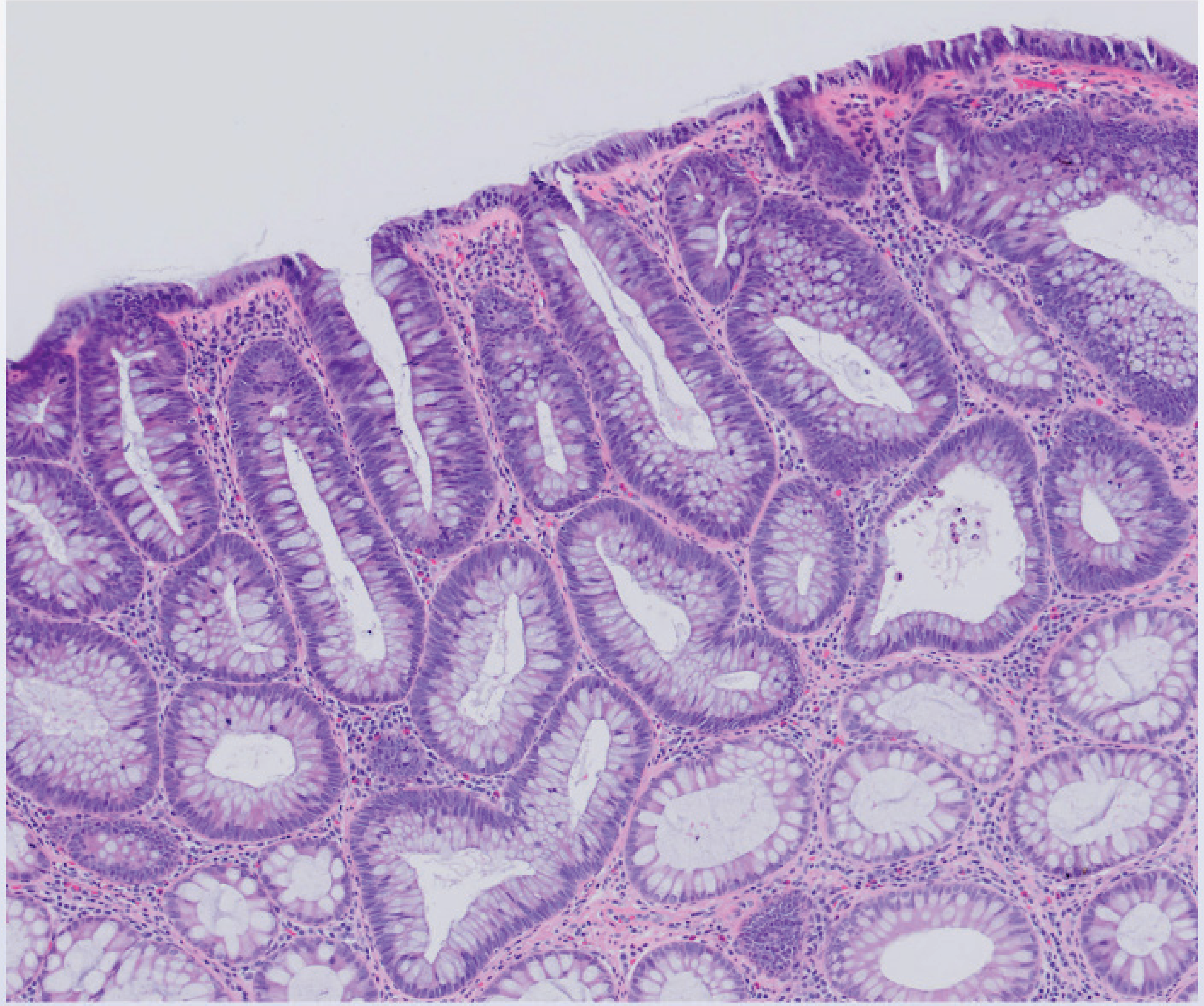


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

The pa

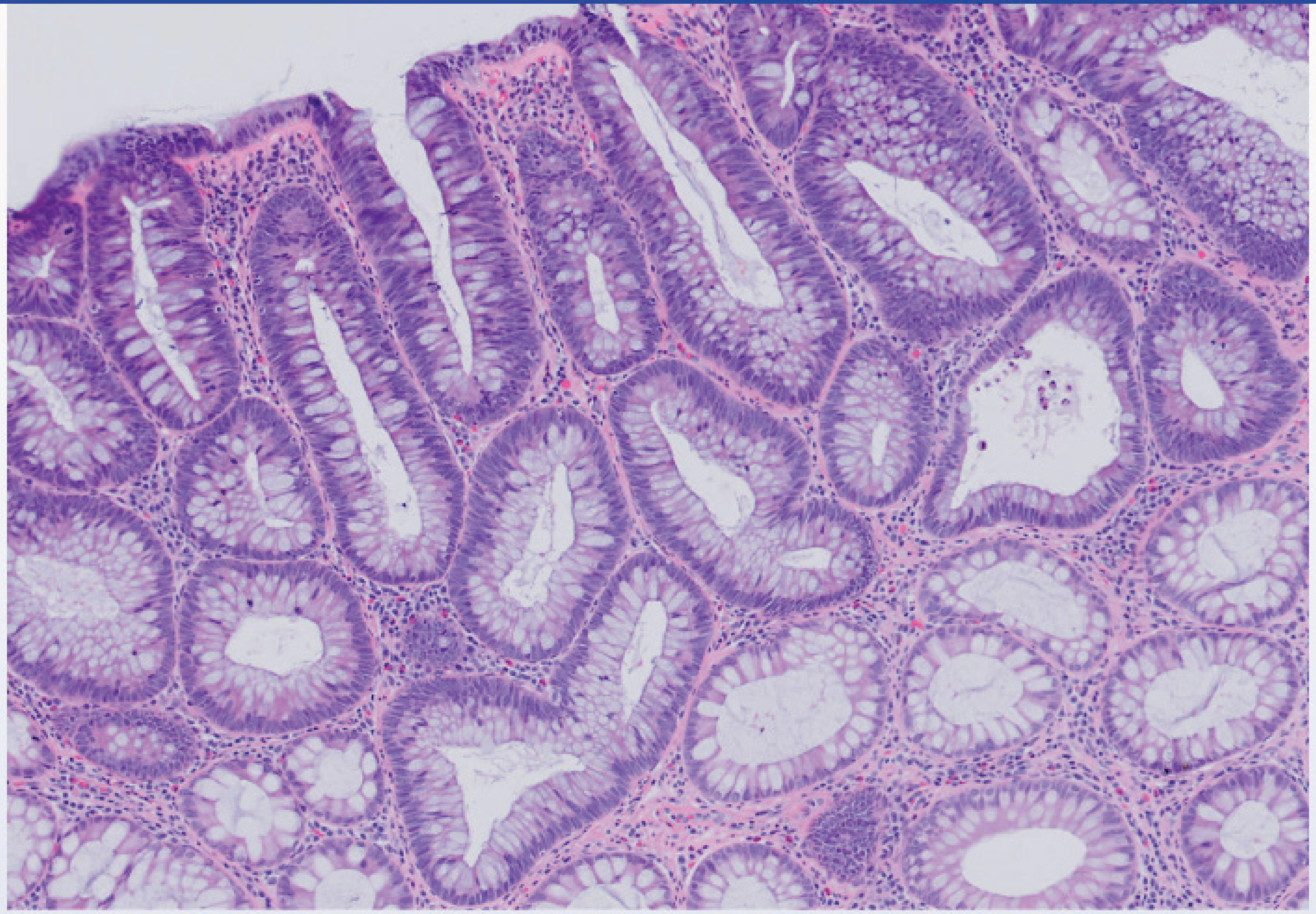
○ A. APC

A 50-year-old man is scheduled to undergo a colonoscopy for routine colorectal cancer screening. He has no abdominal pain, gross blood in the stool, constipation, change in stool caliber, or unintentional weight loss. He also has no family history of colon cancer. The procedure is uncomplicated, but the patient is found to have a small mucosal lesion (~1 cm) in his sigmoid colon. The lesion is biopsied and its histology is shown in the image below.



The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

○ A. APC



The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

○ A. APC

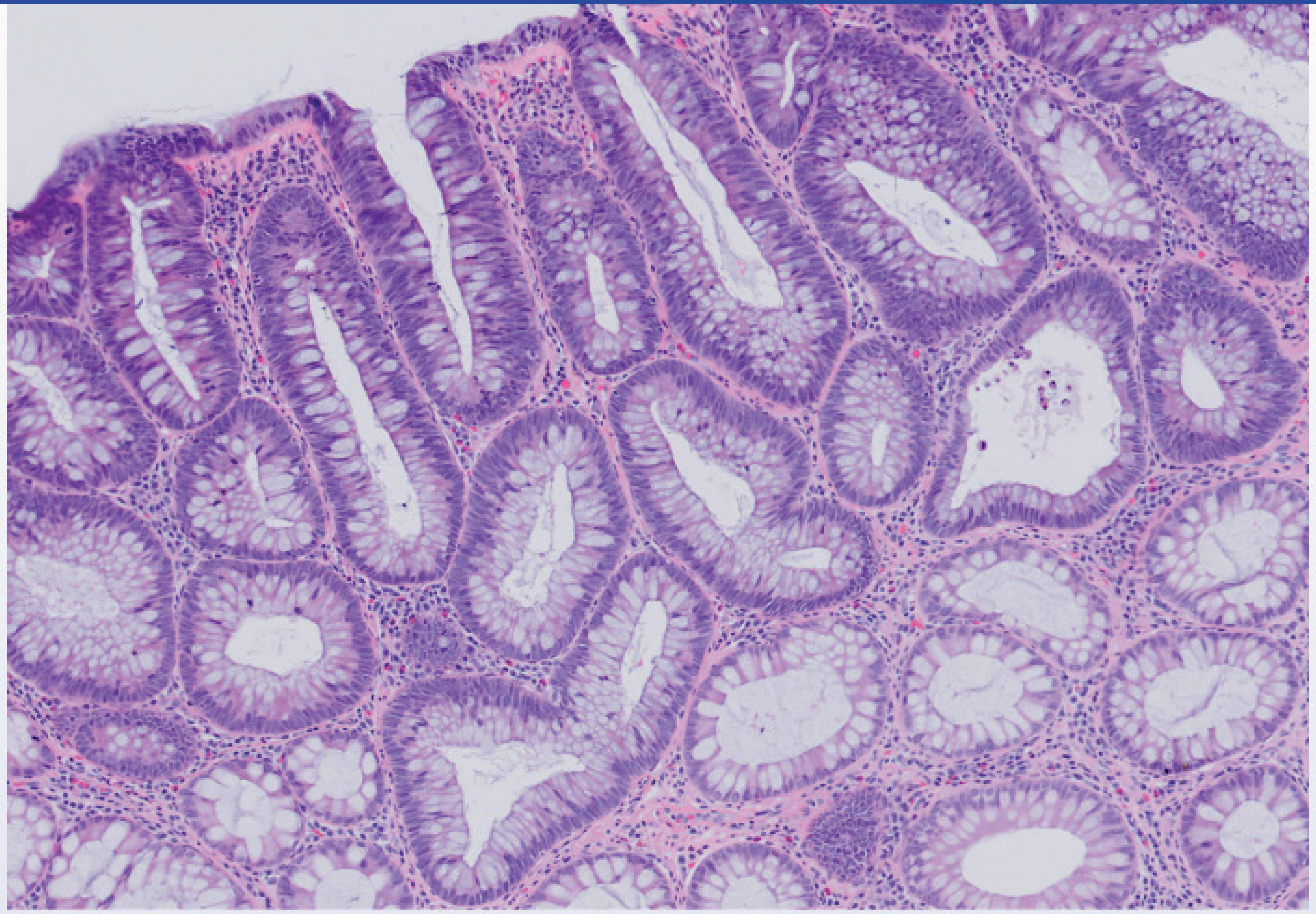
○ B. DCC

○ C. K-RAS

○ D. MSH2

○ E. p53

Submit



The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

✓ ○ A. APC (69%)

○ B. DCC (4%)

✗ ● C. K-RAS (14%)

○ D. MSH2 (7%)

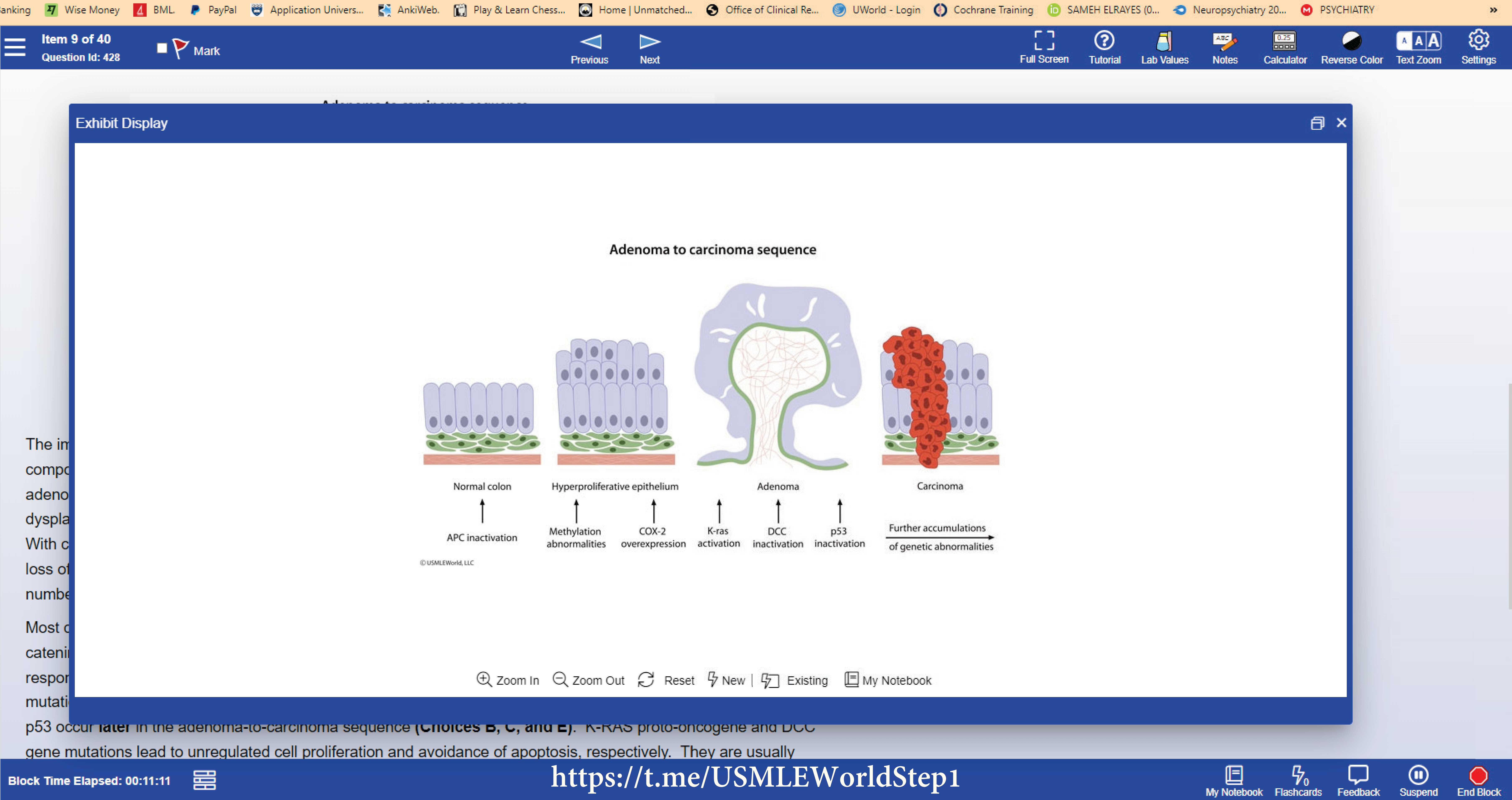
○ E. p53 (4%)

Incorrect
Correct answer
A

69%
Answered correctly

15 secs
Time Spent

2023
Version


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 9 of 40
Question Id: 428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Adenoma to carcinoma sequence
Normal colon
Hyperproliferative epithelium
Adenoma
Carcinoma
APC inactivation
Methylation abnormalities
COX-2 overexpression
K-ras activation
DCC inactivation
p53 inactivation
Further accumulations of genetic abnormalities
© USMLEWorld, LLC
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:11
My Notebook
Flashcards
Feedback
Suspend
End Block

The im

compo

adeno

dyspla

With c

loss of

numbe

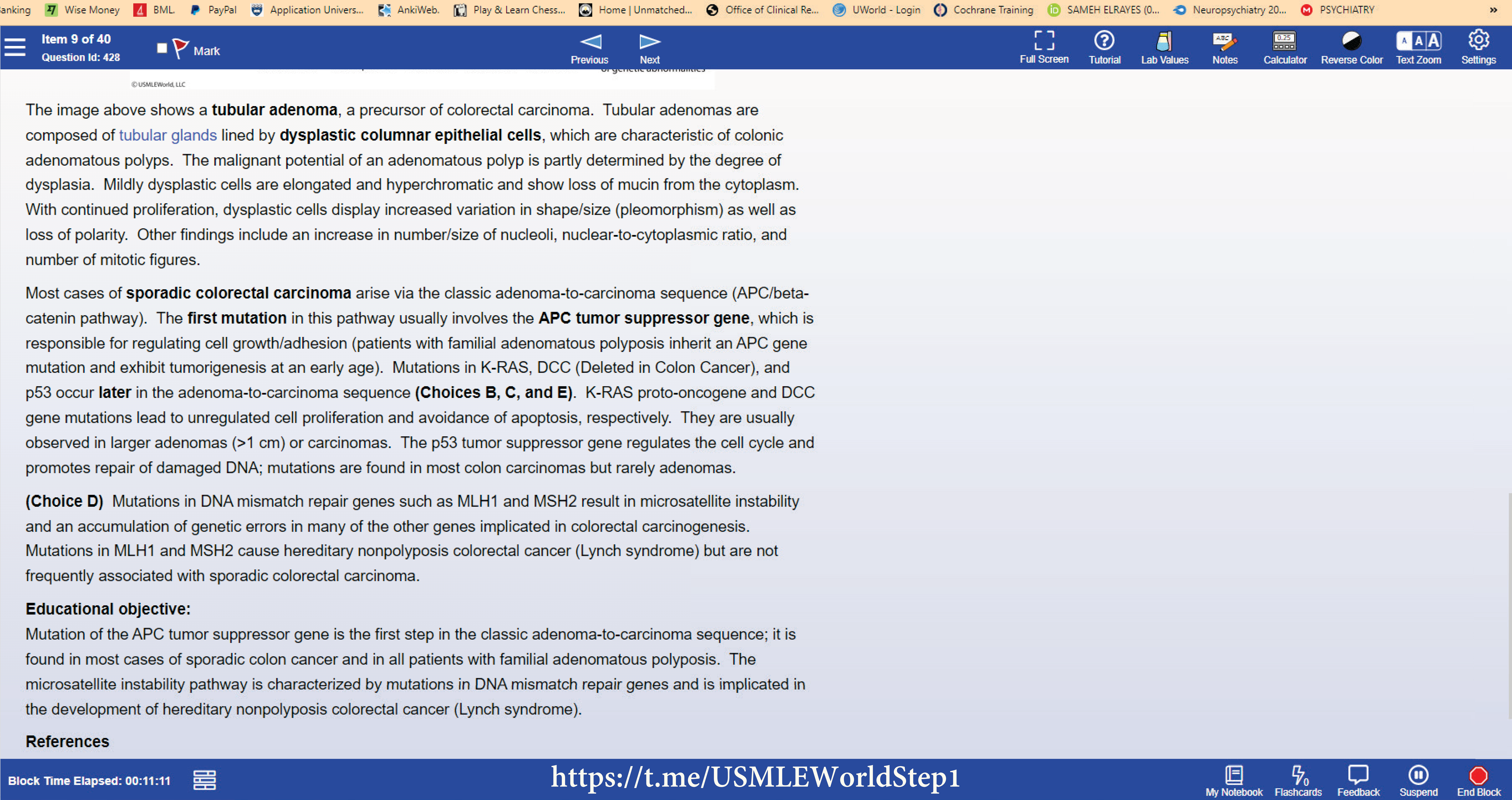
Most c

cateni

respon

mutati

p53 occur **later** in the adenoma-to-carcinoma sequence **(Choices B, C, and E)**. K-RAS proto-oncogene and DCC gene mutations lead to unregulated cell proliferation and avoidance of apoptosis, respectively. They are usually


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 9 of 40
Question Id: 428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
of genetic abnormalities
© USMLEWorld, LLC

The image above shows a **tubular adenoma**, a precursor of colorectal carcinoma. Tubular adenomas are composed of tubular glands lined by **dysplastic columnar epithelial cells**, which are characteristic of colonic adenomatous polyps. The malignant potential of an adenomatous polyp is partly determined by the degree of dysplasia. Mildly dysplastic cells are elongated and hyperchromatic and show loss of mucin from the cytoplasm. With continued proliferation, dysplastic cells display increased variation in shape/size (pleomorphism) as well as loss of polarity. Other findings include an increase in number/size of nucleoli, nuclear-to-cytoplasmic ratio, and number of mitotic figures.

Most cases of **sporadic colorectal carcinoma** arise via the classic adenoma-to-carcinoma sequence (APC/beta-catenin pathway). The **first mutation** in this pathway usually involves the **APC tumor suppressor gene**, which is responsible for regulating cell growth/adhesion (patients with familial adenomatous polyposis inherit an APC gene mutation and exhibit tumorigenesis at an early age). Mutations in K-RAS, DCC (Deleted in Colon Cancer), and p53 occur **later** in the adenoma-to-carcinoma sequence **(Choices B, C, and E)**. K-RAS proto-oncogene and DCC gene mutations lead to unregulated cell proliferation and avoidance of apoptosis, respectively. They are usually observed in larger adenomas (>1 cm) or carcinomas. The p53 tumor suppressor gene regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely adenomas.

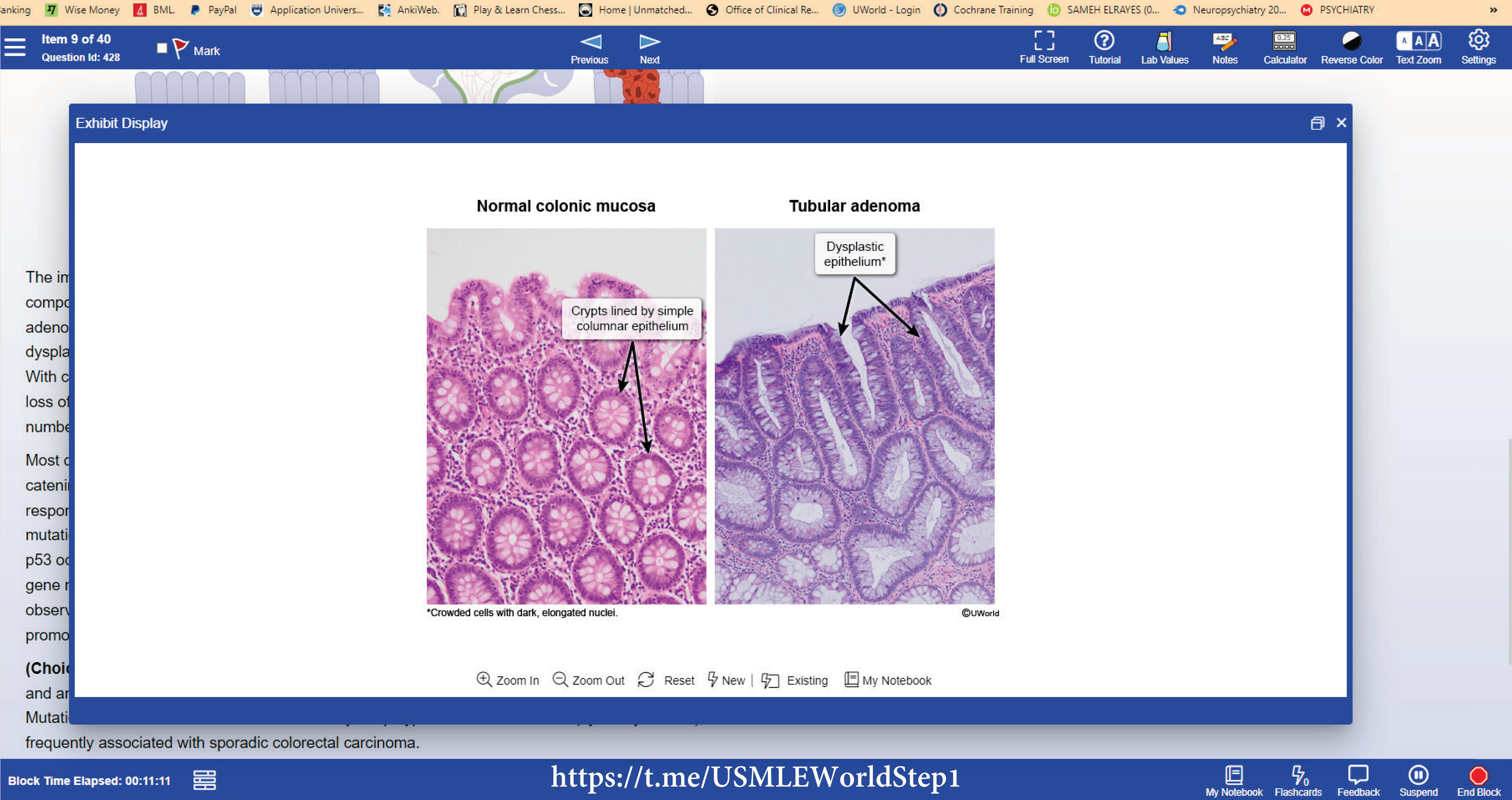
(Choice D) Mutations in DNA mismatch repair genes such as MLH1 and MSH2 result in microsatellite instability and an accumulation of genetic errors in many of the other genes implicated in colorectal carcinogenesis. Mutations in MLH1 and MSH2 cause hereditary nonpolyposis colorectal cancer (Lynch syndrome) but are not frequently associated with sporadic colorectal carcinoma.

Educational objective:

Mutation of the APC tumor suppressor gene is the first step in the classic adenoma-to-carcinoma sequence; it is found in most cases of sporadic colon cancer and in all patients with familial adenomatous polyposis. The microsatellite instability pathway is characterized by mutations in DNA mismatch repair genes and is implicated in the development of hereditary nonpolyposis colorectal cancer (Lynch syndrome).

References

Block Time Elapsed: 00:11:11
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 9 of 40
Question Id: 428
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:11
My Notebook
Flashcards
Feedback
Suspend
End Block

Normal colonic mucosa

Crypts lined by simple columnar epithelium

Tubular adenoma

Dysplastic epithelium*

*Crowded cells with dark, elongated nuclei.

©UWorld

The im

compo

adeno

dyspla

With c

loss of

numbe

Most c

cateni

respor

mutati

p53 oc

gene r

observ

promo

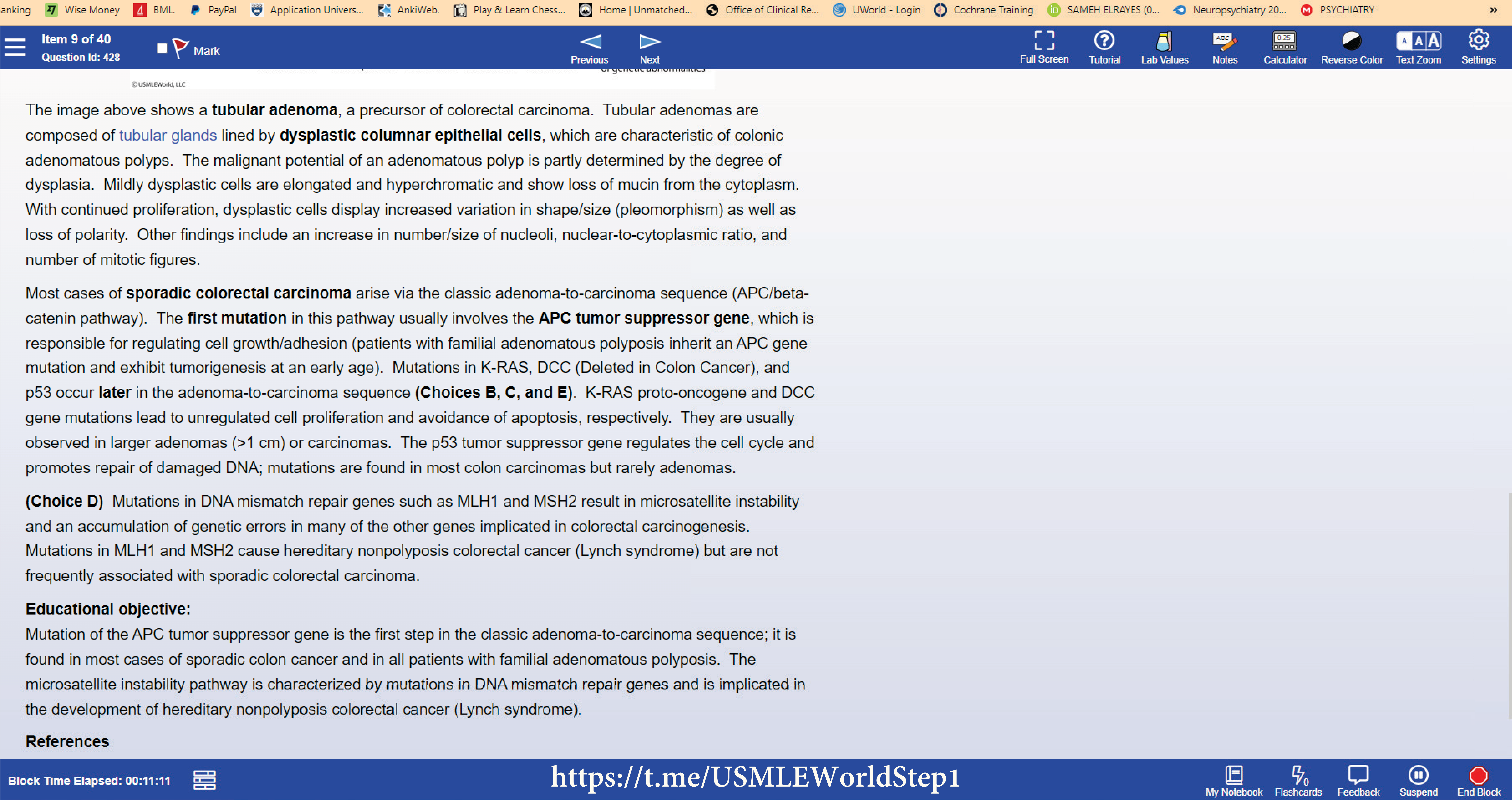
(Choic

and ar

Mutati

frequently associated with sporadic colorectal carcinoma.

https://t.me/USMLEWorldStep1


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 9 of 40
Question Id: 428
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
of genetic abnormalities
© USMLEWorld, LLC

The image above shows a **tubular adenoma**, a precursor of colorectal carcinoma. Tubular adenomas are composed of tubular glands lined by **dysplastic columnar epithelial cells**, which are characteristic of colonic adenomatous polyps. The malignant potential of an adenomatous polyp is partly determined by the degree of dysplasia. Mildly dysplastic cells are elongated and hyperchromatic and show loss of mucin from the cytoplasm. With continued proliferation, dysplastic cells display increased variation in shape/size (pleomorphism) as well as loss of polarity. Other findings include an increase in number/size of nucleoli, nuclear-to-cytoplasmic ratio, and number of mitotic figures.

Most cases of **sporadic colorectal carcinoma** arise via the classic adenoma-to-carcinoma sequence (APC/beta-catenin pathway). The **first mutation** in this pathway usually involves the **APC tumor suppressor gene**, which is responsible for regulating cell growth/adhesion (patients with familial adenomatous polyposis inherit an APC gene mutation and exhibit tumorigenesis at an early age). Mutations in K-RAS, DCC (Deleted in Colon Cancer), and p53 occur **later** in the adenoma-to-carcinoma sequence **(Choices B, C, and E)**. K-RAS proto-oncogene and DCC gene mutations lead to unregulated cell proliferation and avoidance of apoptosis, respectively. They are usually observed in larger adenomas (>1 cm) or carcinomas. The p53 tumor suppressor gene regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely adenomas.

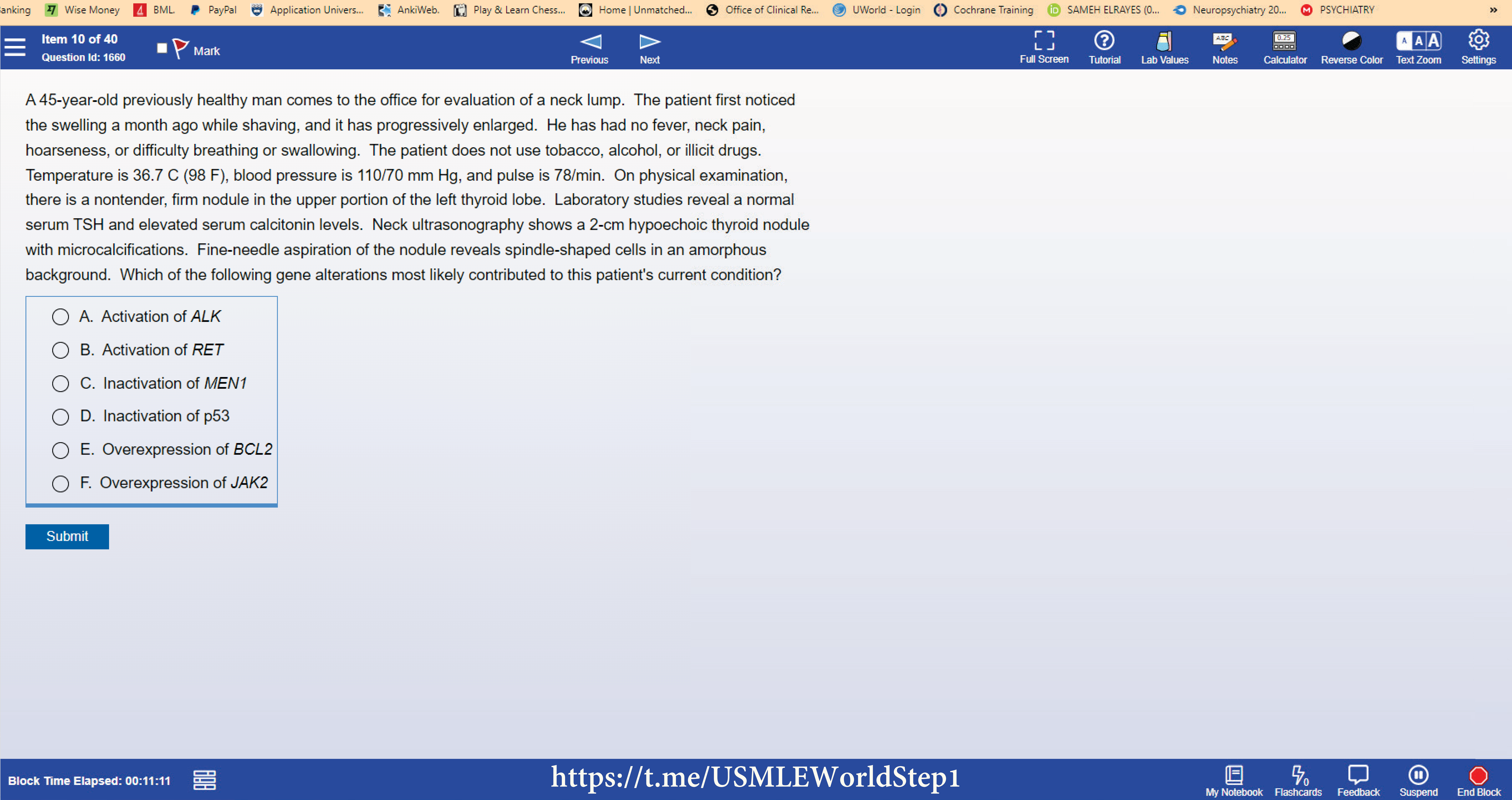
(Choice D) Mutations in DNA mismatch repair genes such as MLH1 and MSH2 result in microsatellite instability and an accumulation of genetic errors in many of the other genes implicated in colorectal carcinogenesis. Mutations in MLH1 and MSH2 cause hereditary nonpolyposis colorectal cancer (Lynch syndrome) but are not frequently associated with sporadic colorectal carcinoma.

Educational objective:

Mutation of the APC tumor suppressor gene is the first step in the classic adenoma-to-carcinoma sequence; it is found in most cases of sporadic colon cancer and in all patients with familial adenomatous polyposis. The microsatellite instability pathway is characterized by mutations in DNA mismatch repair genes and is implicated in the development of hereditary nonpolyposis colorectal cancer (Lynch syndrome).

References

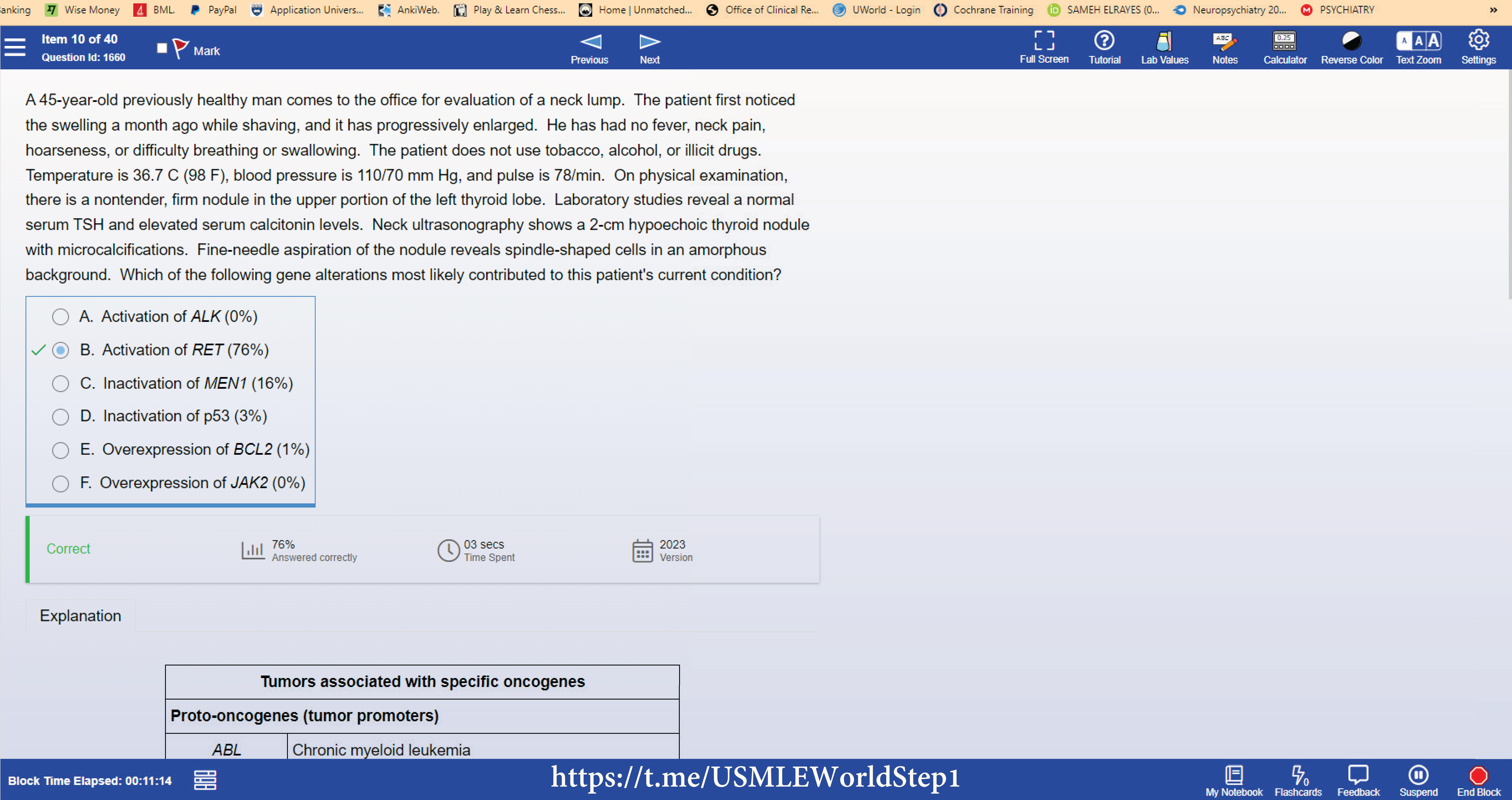
Block Time Elapsed: 00:11:11
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 10 of 40
Question Id: 1660
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 45-year-old previously healthy man comes to the office for evaluation of a neck lump. The patient first noticed the swelling a month ago while shaving, and it has progressively enlarged. He has had no fever, neck pain, hoarseness, or difficulty breathing or swallowing. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the upper portion of the left thyroid lobe. Laboratory studies reveal a normal serum TSH and elevated serum calcitonin levels. Neck ultrasonography shows a 2-cm hypoechoic thyroid nodule with microcalcifications. Fine-needle aspiration of the nodule reveals spindle-shaped cells in an amorphous background. Which of the following gene alterations most likely contributed to this patient's current condition?

○ A. Activation of *ALK*
○ B. Activation of *RET*
○ C. Inactivation of *MEN1*
○ D. Inactivation of p53
○ E. Overexpression of *BCL2*
○ F. Overexpression of *JAK2*

Submit
Block Time Elapsed: 00:11:11
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 10 of 40
Question Id: 1660
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 45-year-old previously healthy man comes to the office for evaluation of a neck lump. The patient first noticed the swelling a month ago while shaving, and it has progressively enlarged. He has had no fever, neck pain, hoarseness, or difficulty breathing or swallowing. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the upper portion of the left thyroid lobe. Laboratory studies reveal a normal serum TSH and elevated serum calcitonin levels. Neck ultrasonography shows a 2-cm hypoechoic thyroid nodule with microcalcifications. Fine-needle aspiration of the nodule reveals spindle-shaped cells in an amorphous background. Which of the following gene alterations most likely contributed to this patient's current condition?

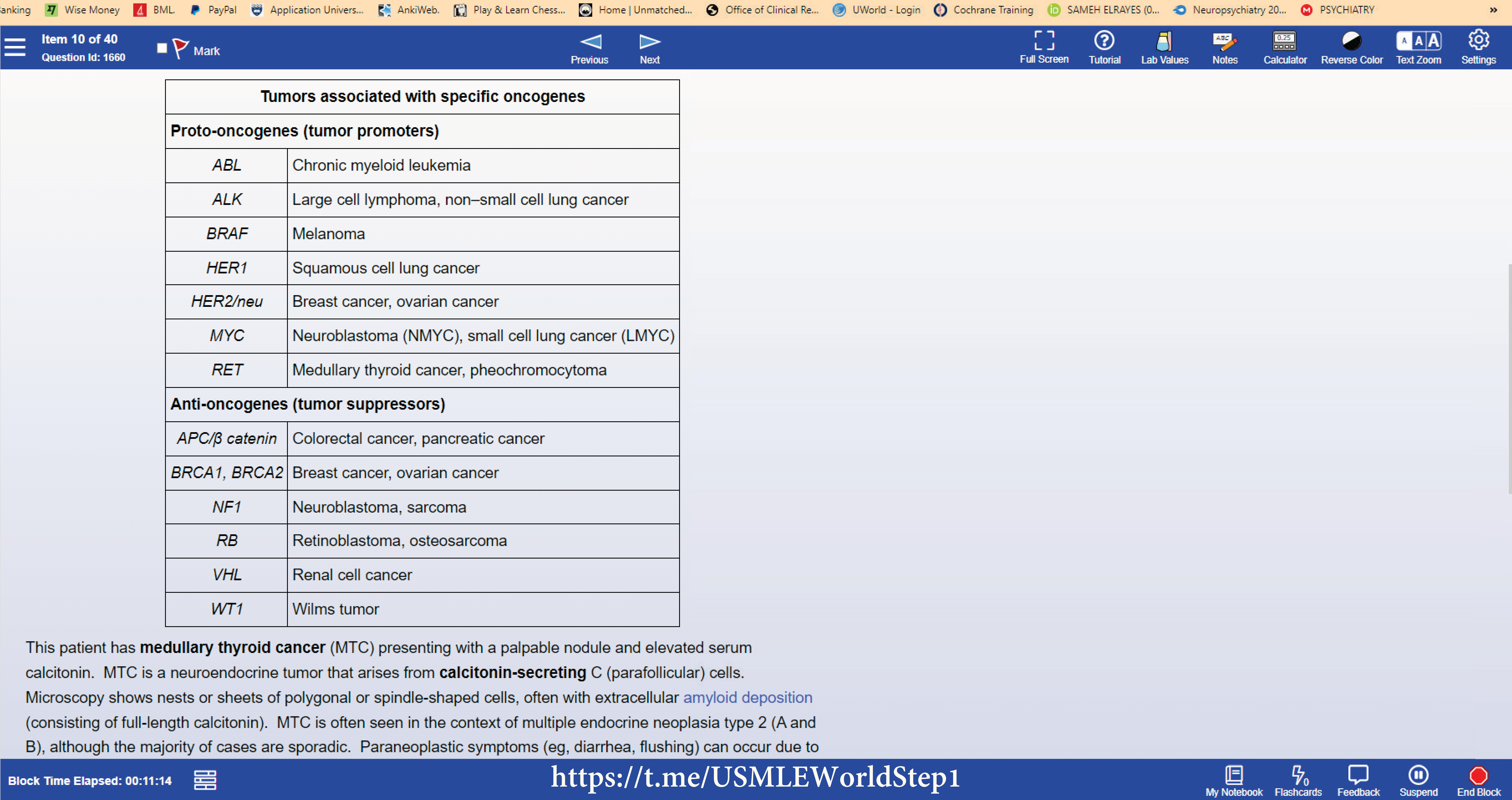
○ A. Activation of *ALK* (0%)
✓ ● B. Activation of *RET* (76%)
○ C. Inactivation of *MEN1* (16%)
○ D. Inactivation of p53 (3%)
○ E. Overexpression of *BCL2* (1%)
○ F. Overexpression of *JAK2* (0%)

Correct
76% Answered correctly
03 secs Time Spent
2023 Version

Explanation

Tumors associated with specific oncogenes	
Proto-oncogenes (tumor promoters)	
ABL	Chronic myeloid leukemia

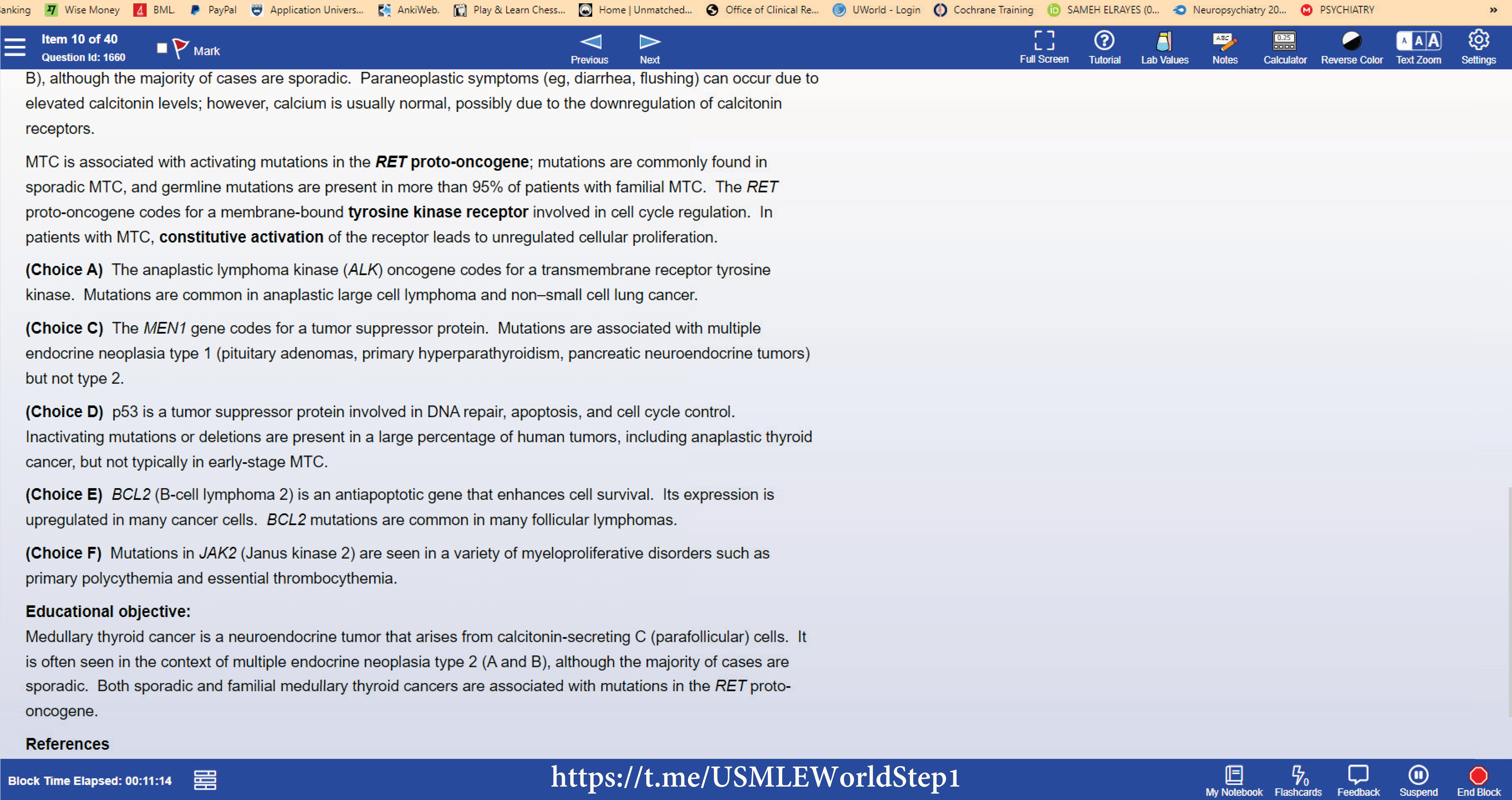
Block Time Elapsed: 00:11:14
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 10 of 40
Question Id: 1660
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Tumors associated with specific oncogenes	
Proto-oncogenes (tumor promoters)	
ABL	Chronic myeloid leukemia
ALK	Large cell lymphoma, non–small cell lung cancer
BRAF	Melanoma
HER1	Squamous cell lung cancer
HER2/neu	Breast cancer, ovarian cancer
MYC	Neuroblastoma (NMYC), small cell lung cancer (LMYC)
RET	Medullary thyroid cancer, pheochromocytoma
Anti-oncogenes (tumor suppressors)	
APC/β catenin	Colorectal cancer, pancreatic cancer
BRCA1, BRCA2	Breast cancer, ovarian cancer
NF1	Neuroblastoma, sarcoma
RB	Retinoblastoma, osteosarcoma
VHL	Renal cell cancer
WT1	Wilms tumor

This patient has **medullary thyroid cancer** (MTC) presenting with a palpable nodule and elevated serum calcitonin. MTC is a neuroendocrine tumor that arises from **calcitonin-secreting** C (parafollicular) cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells, often with extracellular amyloid deposition (consisting of full-length calcitonin). MTC is often seen in the context of multiple endocrine neoplasia type 2 (A and B), although the majority of cases are sporadic. Paraneoplastic symptoms (eg, diarrhea, flushing) can occur due to

Block Time Elapsed: 00:11:14
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 10 of 40
Question Id: 1660
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:14
My Notebook
Flashcards
Feedback
Suspend
End Block

B), although the majority of cases are sporadic. Paraneoplastic symptoms (eg, diarrhea, flushing) can occur due to elevated calcitonin levels; however, calcium is usually normal, possibly due to the downregulation of calcitonin receptors.

MTC is associated with activating mutations in the ***RET* proto-oncogene**; mutations are commonly found in sporadic MTC, and germline mutations are present in more than 95% of patients with familial MTC. The *RET* proto-oncogene codes for a membrane-bound **tyrosine kinase receptor** involved in cell cycle regulation. In patients with MTC, **constitutive activation** of the receptor leads to unregulated cellular proliferation.

(Choice A) The anaplastic lymphoma kinase (*ALK*) oncogene codes for a transmembrane receptor tyrosine kinase. Mutations are common in anaplastic large cell lymphoma and non–small cell lung cancer.

(Choice C) The *MEN1* gene codes for a tumor suppressor protein. Mutations are associated with multiple endocrine neoplasia type 1 (pituitary adenomas, primary hyperparathyroidism, pancreatic neuroendocrine tumors) but not type 2.

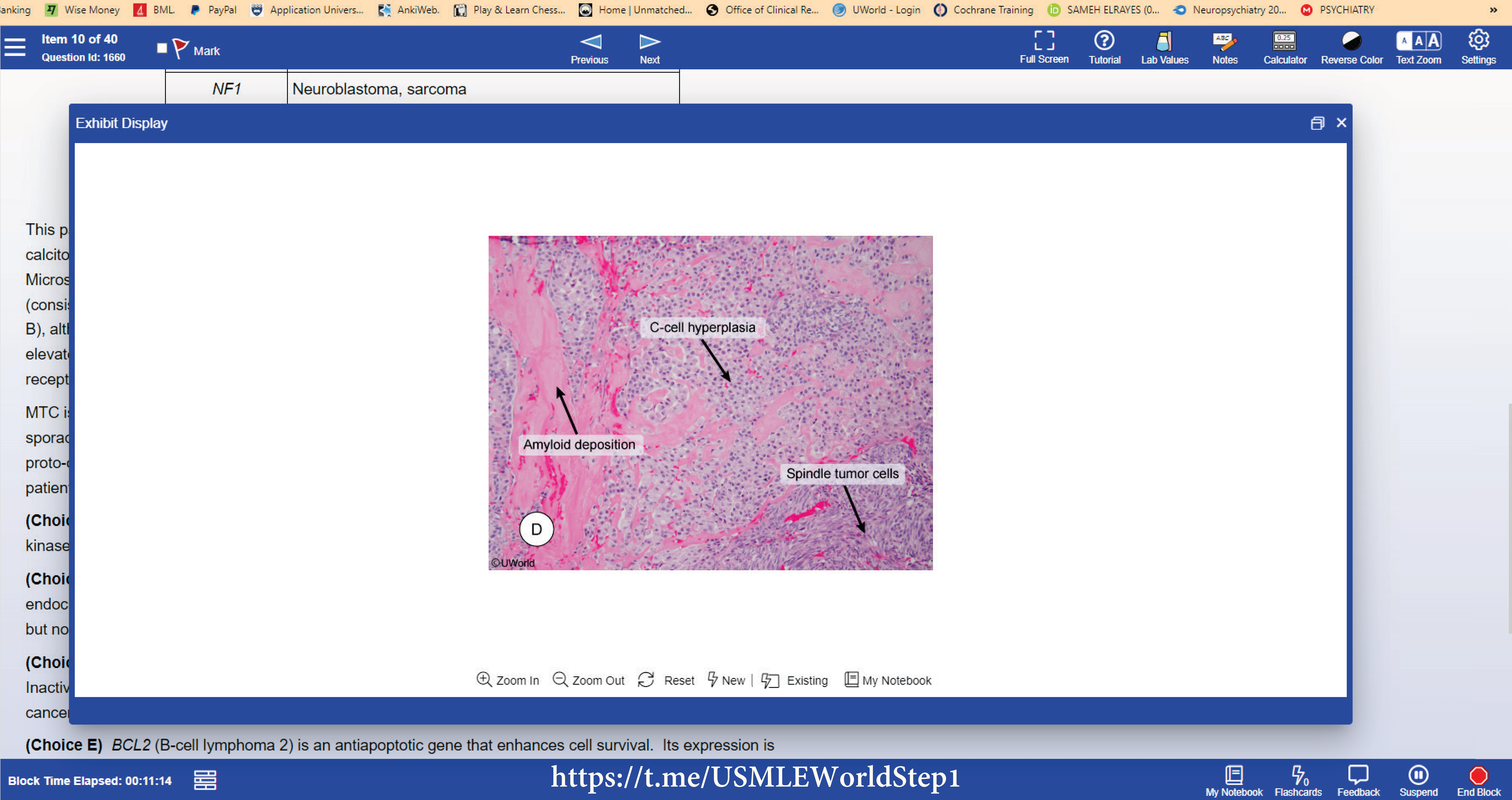
(Choice D) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control. Inactivating mutations or deletions are present in a large percentage of human tumors, including anaplastic thyroid cancer, but not typically in early-stage MTC.

(Choice E) *BCL2* (B-cell lymphoma 2) is an antiapoptotic gene that enhances cell survival. Its expression is upregulated in many cancer cells. *BCL2* mutations are common in many follicular lymphomas.

(Choice F) Mutations in *JAK2* (Janus kinase 2) are seen in a variety of myeloproliferative disorders such as primary polycythemia and essential thrombocythemia.

Educational objective:
Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting C (parafollicular) cells. It is often seen in the context of multiple endocrine neoplasia type 2 (A and B), although the majority of cases are sporadic. Both sporadic and familial medullary thyroid cancers are associated with mutations in the *RET* proto-oncogene.

References


Item 10 of 40
Question Id: 1660
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
C-cell hyperplasia
Amyloid deposition
Spindle tumor cells
D
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:14
My Notebook
Flashcards
Feedback
Suspend
End Block

NF1	Neuroblastoma, sarcoma

This p
calcito
Micros
(consi
B), alt
elevat
recept

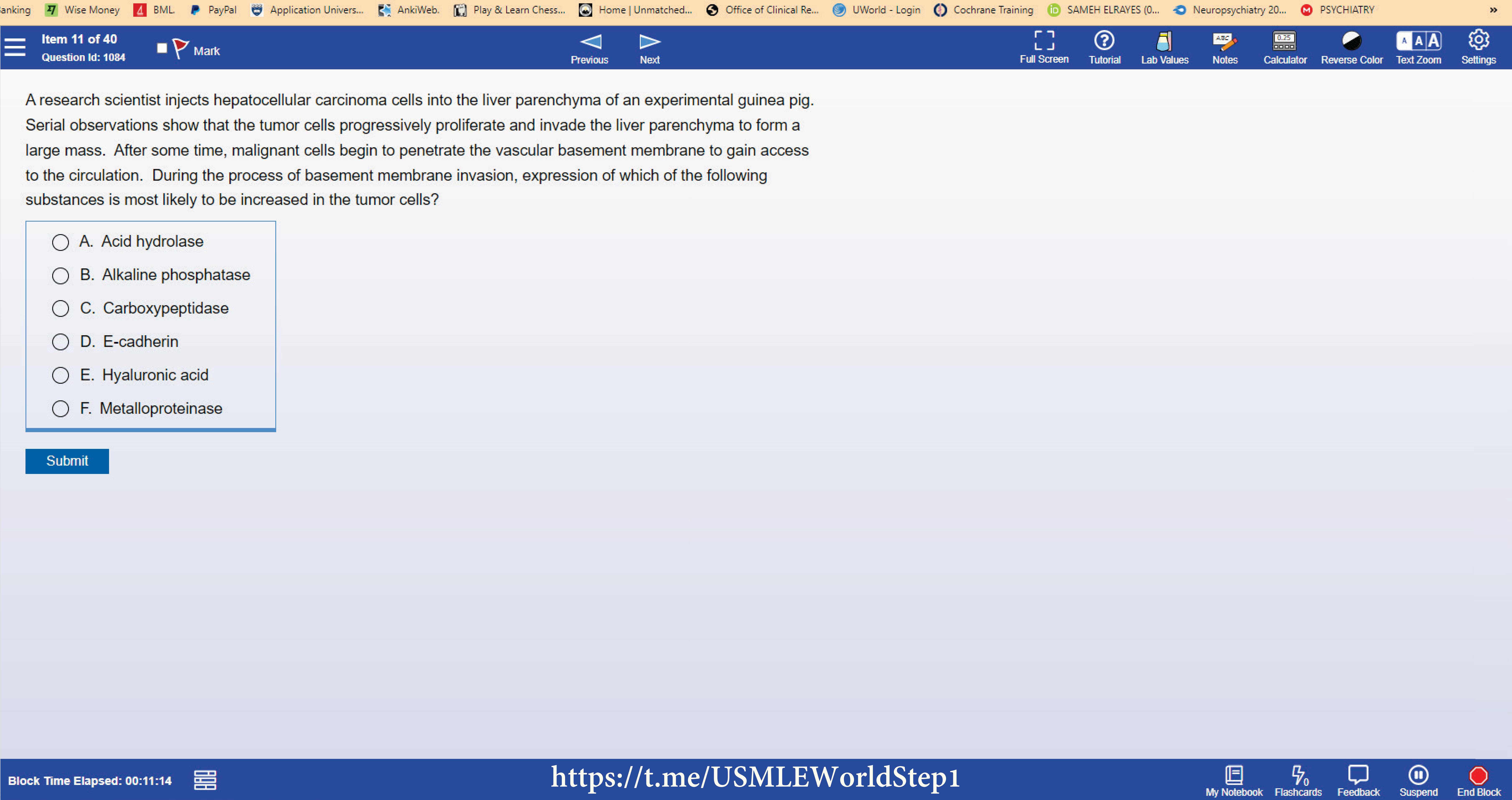
MTC i
sporad
proto-
patien

(Choic
kinase

(Choic
endoc
but no

(Choic
Inactiv
cance

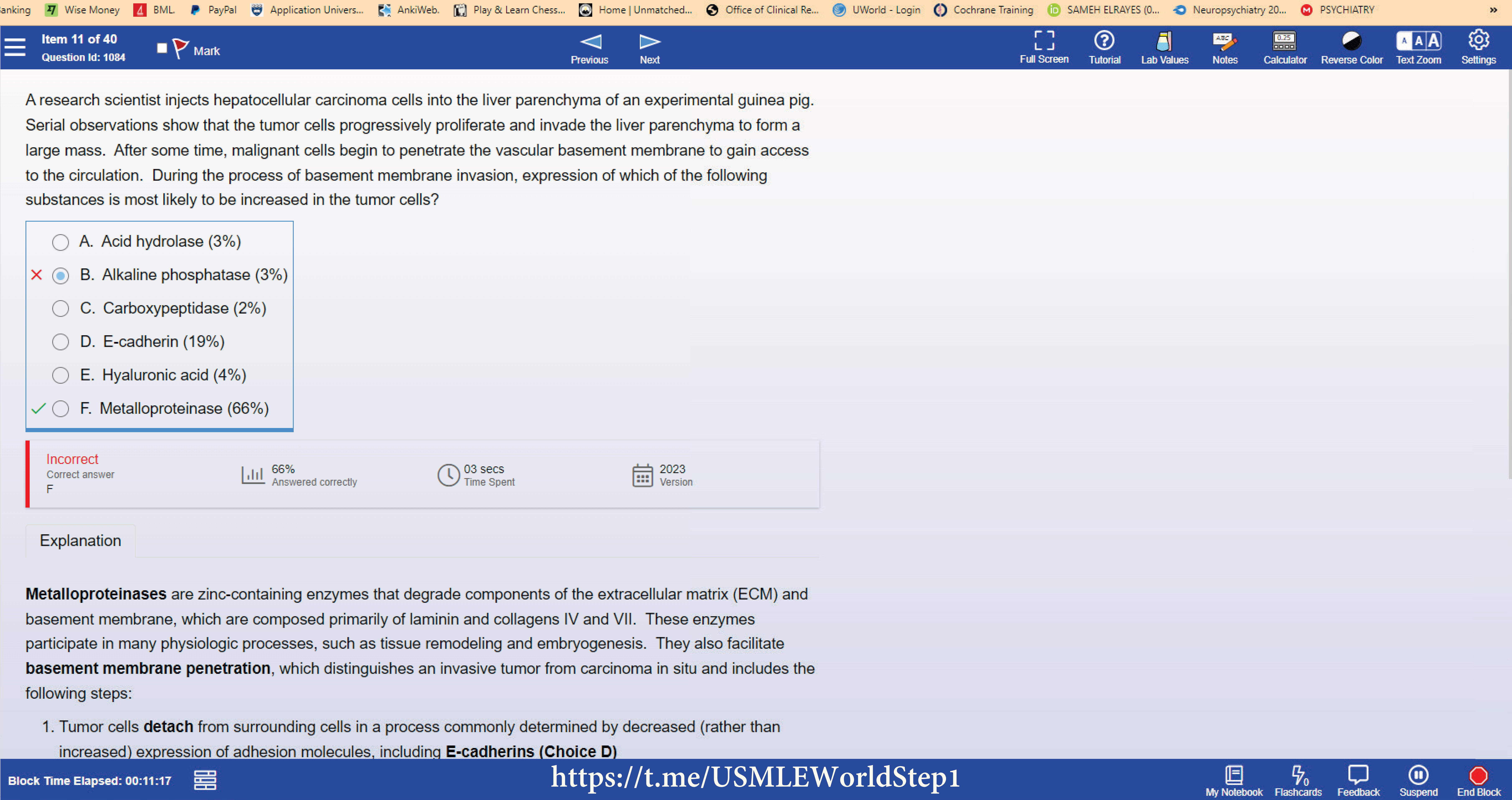
(Choice E) *BCL2* (B-cell lymphoma 2) is an antiapoptotic gene that enhances cell survival. Its expression is


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 11 of 40
Question Id: 1084
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:14
My Notebook
Flashcards
Feedback
Suspend
End Block

A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

- ○ A. Acid hydrolase
- ○ B. Alkaline phosphatase
- ○ C. Carboxypeptidase
- ○ D. E-cadherin
- ○ E. Hyaluronic acid
- ○ F. Metalloproteinase

Submit


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 11 of 40
Question Id: 1084
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

○ A. Acid hydrolase (3%)
✗ ● B. Alkaline phosphatase (3%)
○ C. Carboxypeptidase (2%)
○ D. E-cadherin (19%)
○ E. Hyaluronic acid (4%)
✓ ○ F. Metalloproteinase (66%)

Incorrect
Correct answer
F

66%
Answered correctly

03 secs
Time Spent

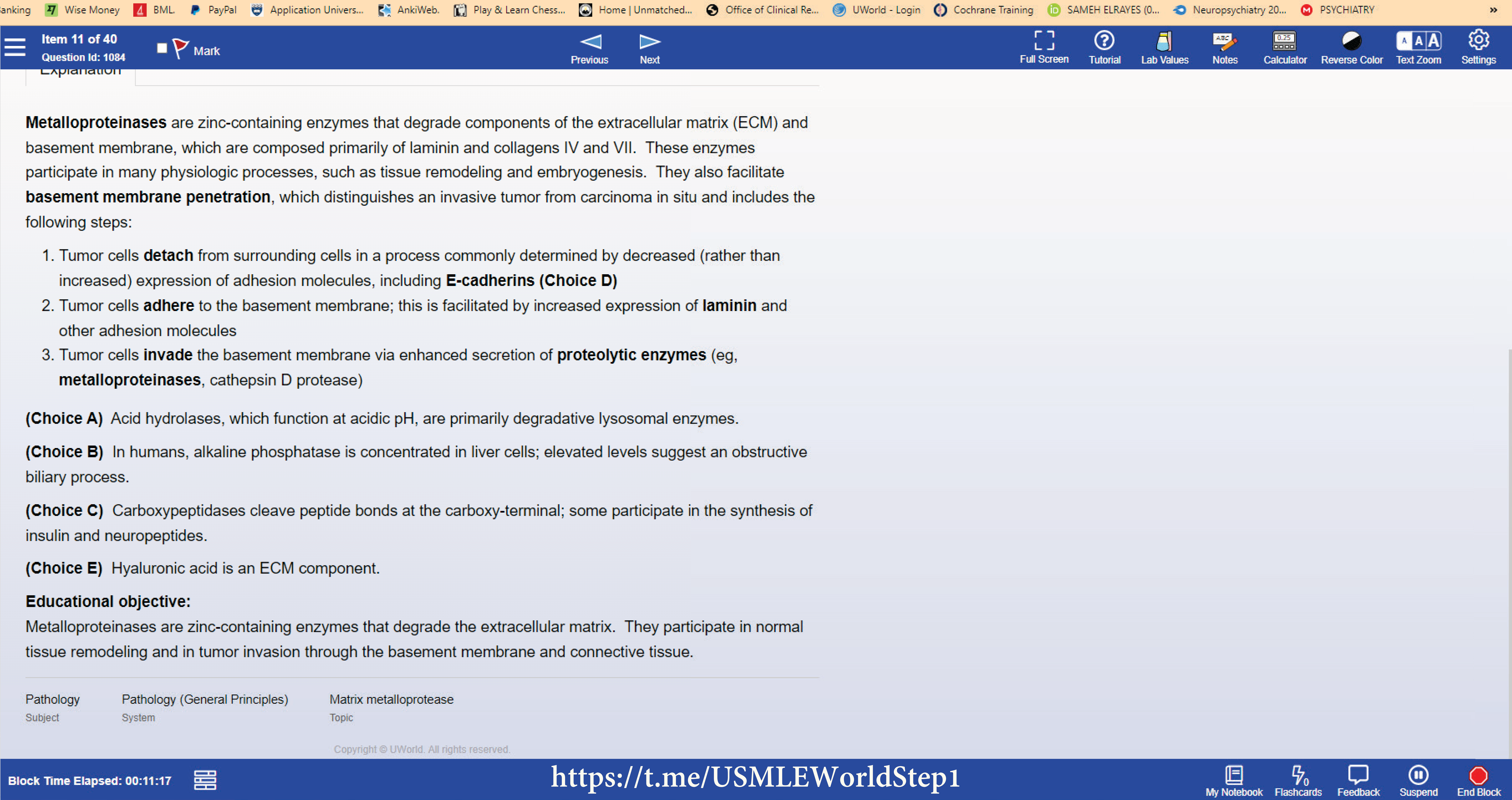
2023
Version

Explanation

Metalloproteinases are zinc-containing enzymes that degrade components of the extracellular matrix (ECM) and basement membrane, which are composed primarily of laminin and collagens IV and VII. These enzymes participate in many physiologic processes, such as tissue remodeling and embryogenesis. They also facilitate **basement membrane penetration**, which distinguishes an invasive tumor from carcinoma in situ and includes the following steps:

1. Tumor cells **detach** from surrounding cells in a process commonly determined by decreased (rather than increased) expression of adhesion molecules, including **E-cadherins (Choice D)**

Block Time Elapsed: 00:11:17
https://t.me/USMLEWorldStep1
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 11 of 40
Question Id: 1084
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:11:17
My Notebook
Flashcards
Feedback
Suspend
End Block

Metalloproteinases are zinc-containing enzymes that degrade components of the extracellular matrix (ECM) and basement membrane, which are composed primarily of laminin and collagens IV and VII. These enzymes participate in many physiologic processes, such as tissue remodeling and embryogenesis. They also facilitate **basement membrane penetration**, which distinguishes an invasive tumor from carcinoma in situ and includes the following steps:

1. Tumor cells **detach** from surrounding cells in a process commonly determined by decreased (rather than increased) expression of adhesion molecules, including **E-cadherins (Choice D)**
2. Tumor cells **adhere** to the basement membrane; this is facilitated by increased expression of **laminin** and other adhesion molecules
3. Tumor cells **invade** the basement membrane via enhanced secretion of **proteolytic enzymes** (eg, **metalloproteinases**, cathepsin D protease)

(Choice A) Acid hydrolases, which function at acidic pH, are primarily degradative lysosomal enzymes.

(Choice B) In humans, alkaline phosphatase is concentrated in liver cells; elevated levels suggest an obstructive biliary process.

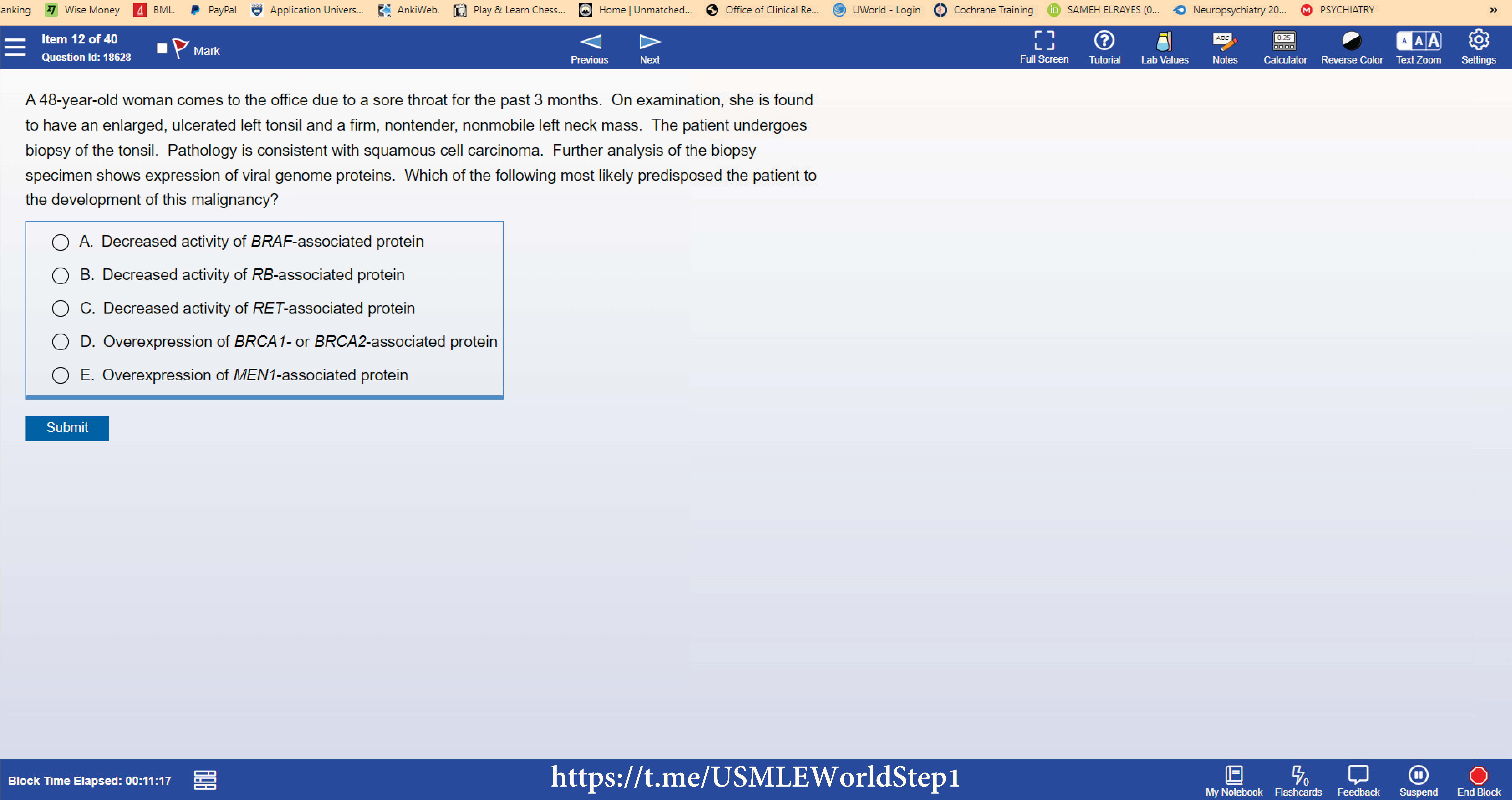
(Choice C) Carboxypeptidases cleave peptide bonds at the carboxy-terminal; some participate in the synthesis of insulin and neuropeptides.

(Choice E) Hyaluronic acid is an ECM component.

Educational objective:
Metalloproteinases are zinc-containing enzymes that degrade the extracellular matrix. They participate in normal tissue remodeling and in tumor invasion through the basement membrane and connective tissue.

Pathology	Pathology (General Principles)	Matrix metalloprotease
Subject	System	Topic

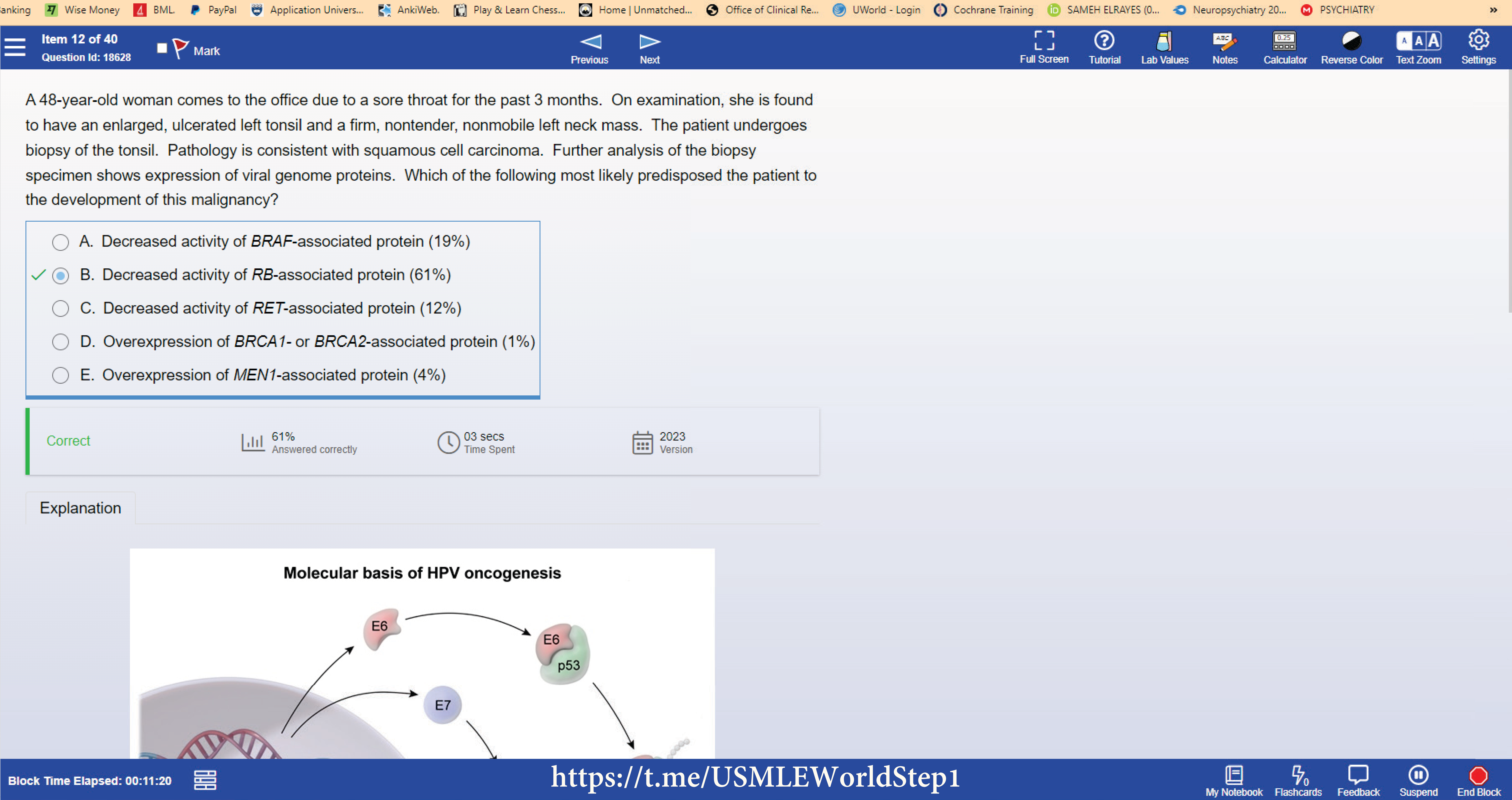
Copyright © UWorld. All rights reserved.


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 48-year-old woman comes to the office due to a sore throat for the past 3 months. On examination, she is found to have an enlarged, ulcerated left tonsil and a firm, nontender, nonmobile left neck mass. The patient undergoes biopsy of the tonsil. Pathology is consistent with squamous cell carcinoma. Further analysis of the biopsy specimen shows expression of viral genome proteins. Which of the following most likely predisposed the patient to the development of this malignancy?

○ A. Decreased activity of *BRAF*-associated protein
○ B. Decreased activity of *RB*-associated protein
○ C. Decreased activity of *RET*-associated protein
○ D. Overexpression of *BRCA1*- or *BRCA2*-associated protein
○ E. Overexpression of *MEN1*-associated protein

Submit
Block Time Elapsed: 00:11:17
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 48-year-old woman comes to the office due to a sore throat for the past 3 months. On examination, she is found to have an enlarged, ulcerated left tonsil and a firm, nontender, nonmobile left neck mass. The patient undergoes biopsy of the tonsil. Pathology is consistent with squamous cell carcinoma. Further analysis of the biopsy specimen shows expression of viral genome proteins. Which of the following most likely predisposed the patient to the development of this malignancy?

○ A. Decreased activity of *BRAF*-associated protein (19%)

✓ ● B. Decreased activity of *RB*-associated protein (61%)

○ C. Decreased activity of *RET*-associated protein (12%)

○ D. Overexpression of *BRCA1*- or *BRCA2*-associated protein (1%)

○ E. Overexpression of *MEN1*-associated protein (4%)

Correct

61% Answered correctly

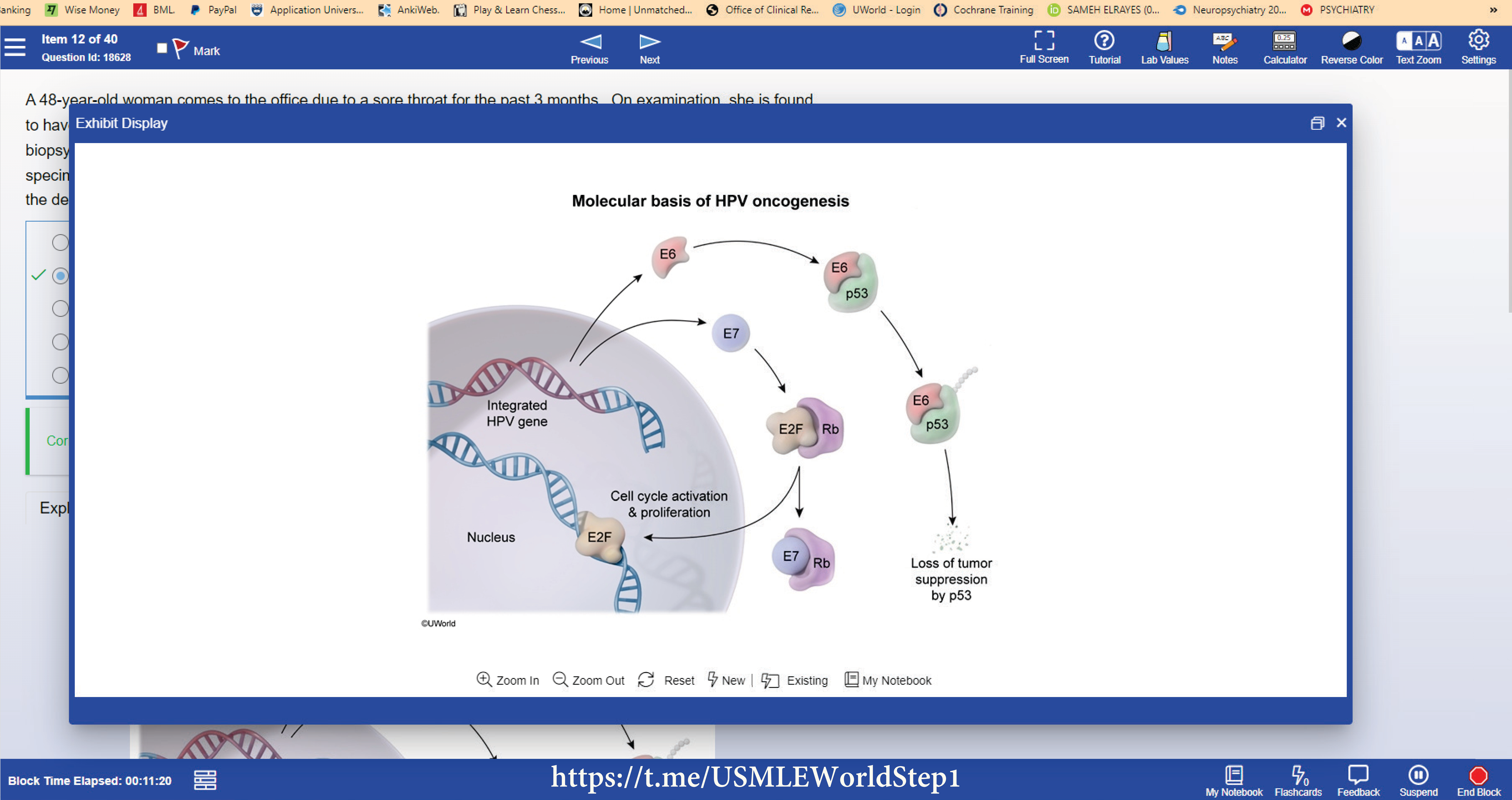
03 secs Time Spent

2023 Version

Explanation

Molecular basis of HPV oncogenesis

E6
E6
p53
E7
Block Time Elapsed: 00:11:20
https://t.me/USMLEWorldStep1
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 48-year-old woman comes to the office due to a sore throat for the past 3 months. On examination, she is found

to hav

biopsy

specin

the de

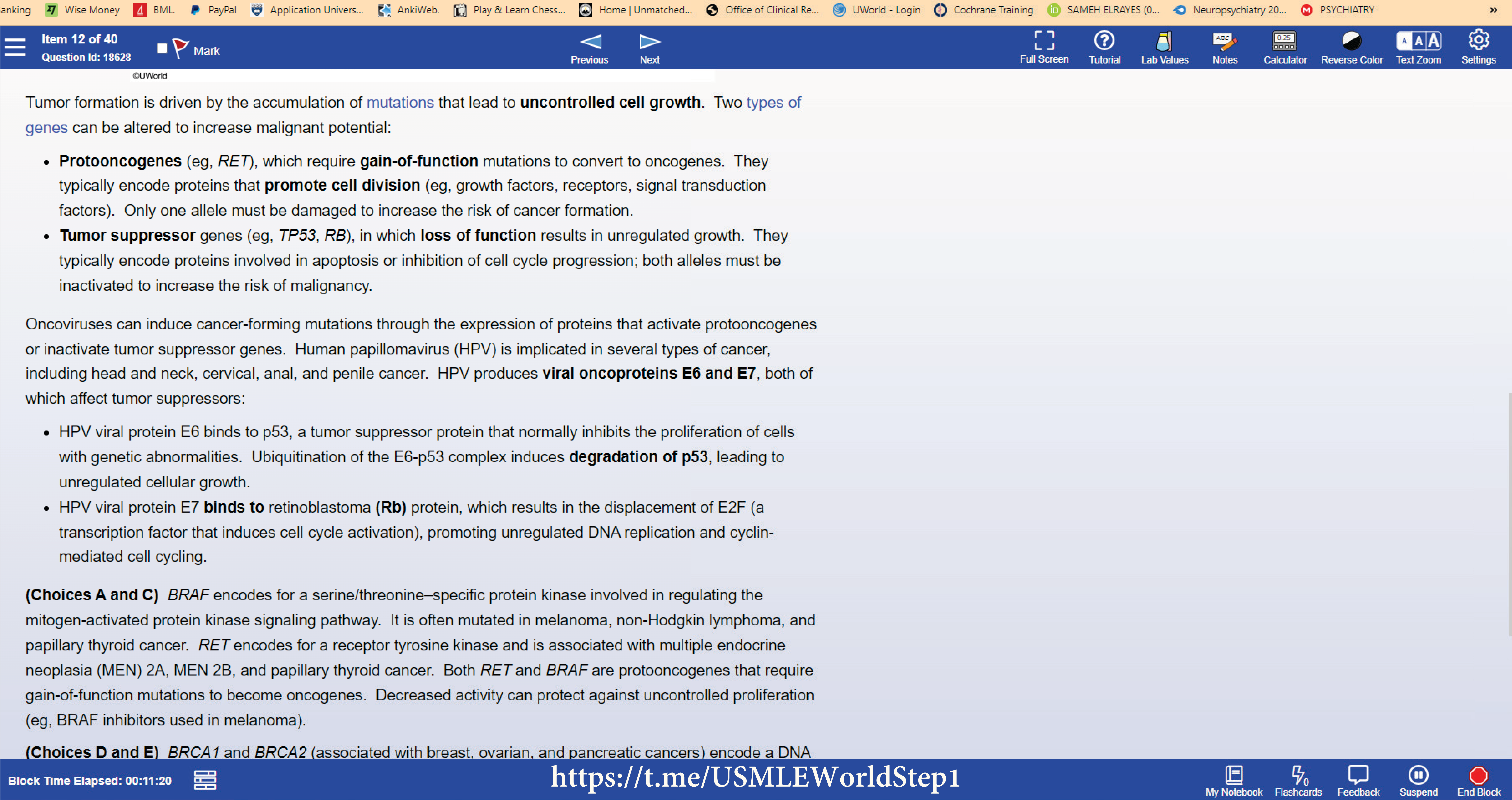
Cor
Expl
Exhibit Display

Molecular basis of HPV oncogenesis

E6
E6
p53
E7
E2F
Rb
E6
p53
Integrated
HPV gene
Cell cycle activation
& proliferation
Nucleus
E2F
E7
Rb
Loss of tumor
suppression
by p53
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:11:20

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Block Time Elapsed: 00:11:20
My Notebook
Flashcards
Feedback
Suspend
End Block

Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two types of genes can be altered to increase malignant potential:

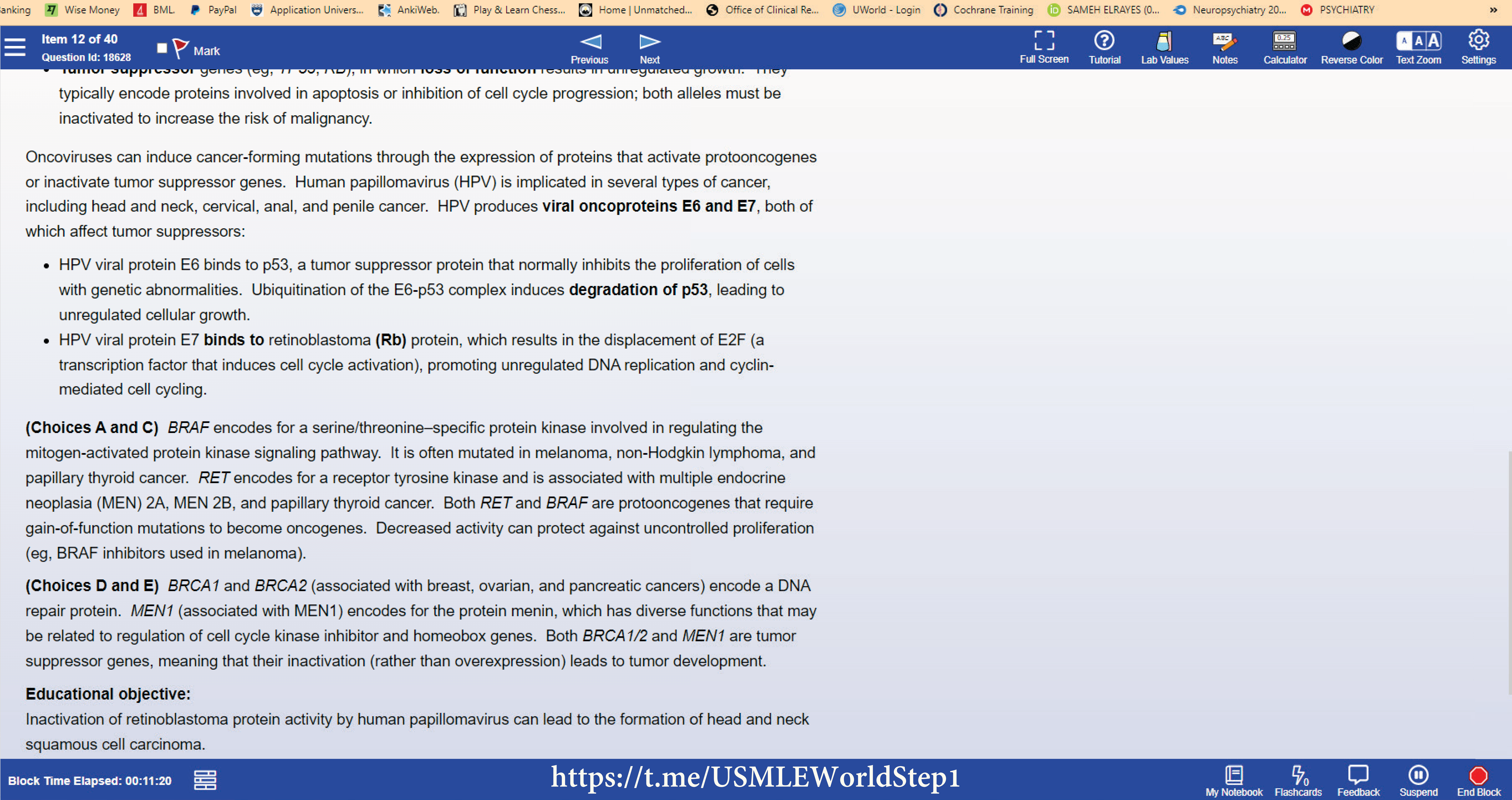
- **Protooncogenes** (eg, *RET*), which require **gain-of-function** mutations to convert to oncogenes. They typically encode proteins that **promote cell division** (eg, growth factors, receptors, signal transduction factors). Only one allele must be damaged to increase the risk of cancer formation.
- **Tumor suppressor** genes (eg, *TP53*, *RB*), in which **loss of function** results in unregulated growth. They typically encode proteins involved in apoptosis or inhibition of cell cycle progression; both alleles must be inactivated to increase the risk of malignancy.

Oncoviruses can induce cancer-forming mutations through the expression of proteins that activate protooncogenes or inactivate tumor suppressor genes. Human papillomavirus (HPV) is implicated in several types of cancer, including head and neck, cervical, anal, and penile cancer. HPV produces **viral oncoproteins E6 and E7**, both of which affect tumor suppressors:

- HPV viral protein E6 binds to p53, a tumor suppressor protein that normally inhibits the proliferation of cells with genetic abnormalities. Ubiquitination of the E6-p53 complex induces **degradation of p53**, leading to unregulated cellular growth.
- HPV viral protein E7 **binds to** retinoblastoma **(Rb)** protein, which results in the displacement of E2F (a transcription factor that induces cell cycle activation), promoting unregulated DNA replication and cyclin-mediated cell cycling.

(Choices A and C) *BRAF* encodes for a serine/threonine–specific protein kinase involved in regulating the mitogen-activated protein kinase signaling pathway. It is often mutated in melanoma, non-Hodgkin lymphoma, and papillary thyroid cancer. *RET* encodes for a receptor tyrosine kinase and is associated with multiple endocrine neoplasia (MEN) 2A, MEN 2B, and papillary thyroid cancer. Both *RET* and *BRAF* are protooncogenes that require gain-of-function mutations to become oncogenes. Decreased activity can protect against uncontrolled proliferation (eg, BRAF inhibitors used in melanoma).

(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:20
My Notebook
Flashcards
Feedback
Suspend
End Block

- **Tumor suppressor** genes (eg, *TP53*, *RB*), in which **loss of function** results in unregulated growth. They typically encode proteins involved in apoptosis or inhibition of cell cycle progression; both alleles must be inactivated to increase the risk of malignancy.

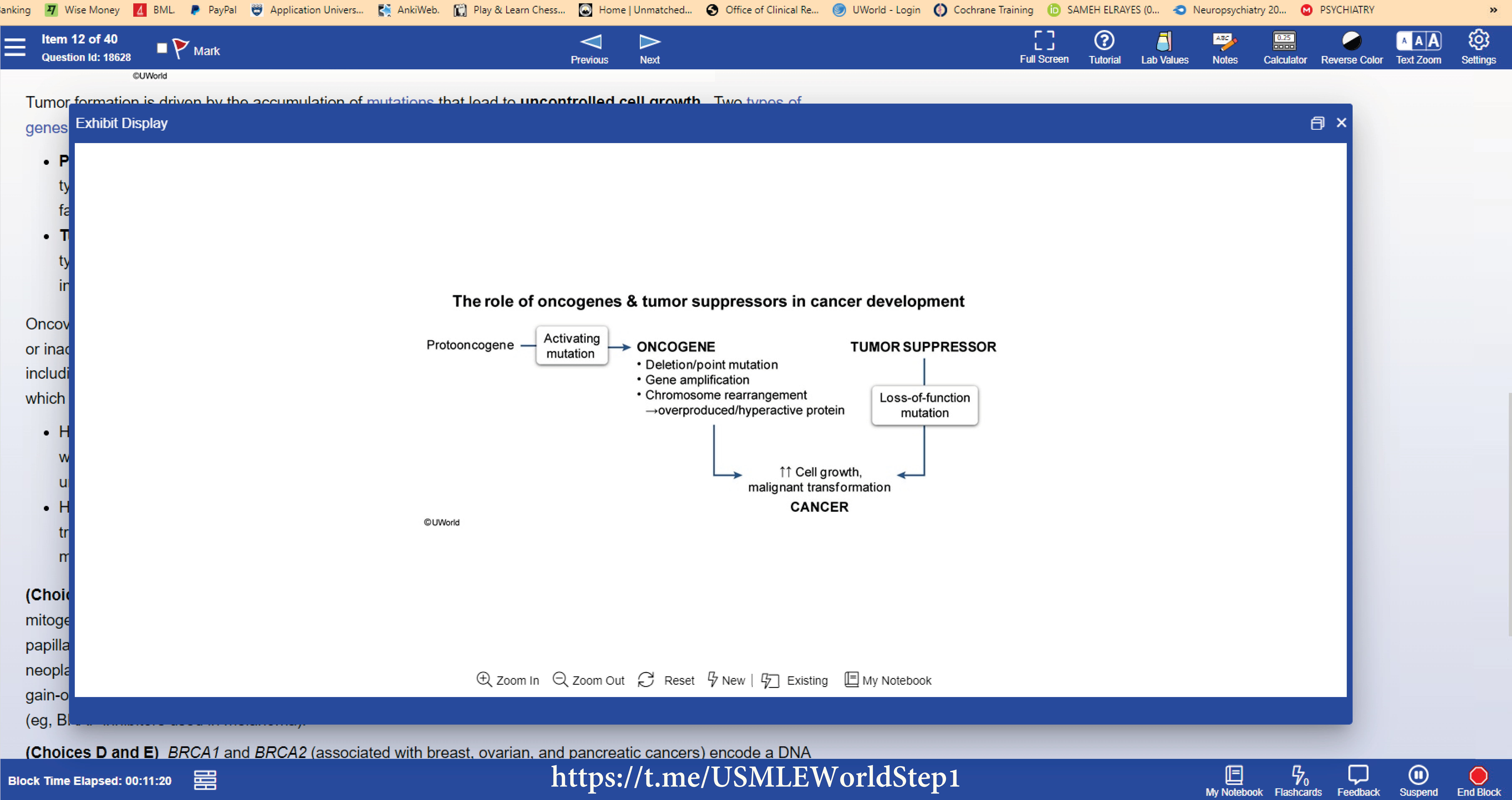
Oncoviruses can induce cancer-forming mutations through the expression of proteins that activate protooncogenes or inactivate tumor suppressor genes. Human papillomavirus (HPV) is implicated in several types of cancer, including head and neck, cervical, anal, and penile cancer. HPV produces **viral oncoproteins E6 and E7**, both of which affect tumor suppressors:

- HPV viral protein E6 binds to p53, a tumor suppressor protein that normally inhibits the proliferation of cells with genetic abnormalities. Ubiquitination of the E6-p53 complex induces **degradation of p53**, leading to unregulated cellular growth.
- HPV viral protein E7 **binds to** retinoblastoma **(Rb)** protein, which results in the displacement of E2F (a transcription factor that induces cell cycle activation), promoting unregulated DNA replication and cyclin-mediated cell cycling.

(Choices A and C) *BRAF* encodes for a serine/threonine–specific protein kinase involved in regulating the mitogen-activated protein kinase signaling pathway. It is often mutated in melanoma, non-Hodgkin lymphoma, and papillary thyroid cancer. *RET* encodes for a receptor tyrosine kinase and is associated with multiple endocrine neoplasia (MEN) 2A, MEN 2B, and papillary thyroid cancer. Both *RET* and *BRAF* are protooncogenes that require gain-of-function mutations to become oncogenes. Decreased activity can protect against uncontrolled proliferation (eg, BRAF inhibitors used in melanoma).

(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA repair protein. *MEN1* (associated with MEN1) encodes for the protein menin, which has diverse functions that may be related to regulation of cell cycle kinase inhibitor and homeobox genes. Both *BRCA1/2* and *MEN1* are tumor suppressor genes, meaning that their inactivation (rather than overexpression) leads to tumor development.

Educational objective:
Inactivation of retinoblastoma protein activity by human papillomavirus can lead to the formation of head and neck squamous cell carcinoma.


Item 12 of 40
Question Id: 18628
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:20
My Notebook
Flashcards
Feedback
Suspend
End Block

Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two types of

The role of oncogenes & tumor suppressors in cancer development

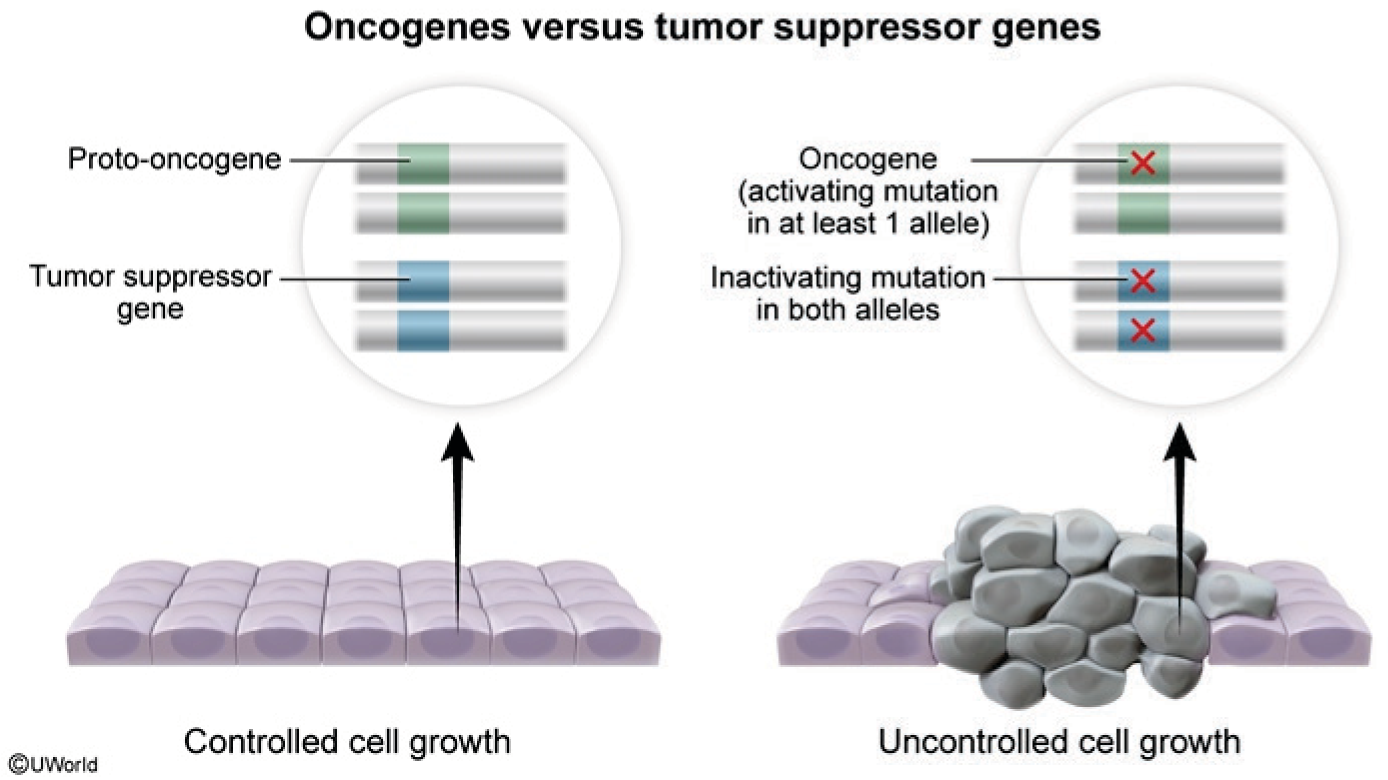
Protooncogene
Activating mutation
ONCOGENE
• Deletion/point mutation
• Gene amplification
• Chromosome rearrangement
→overproduced/hyperactive protein
TUMOR SUPPRESSOR
Loss-of-function mutation
↑↑ Cell growth,
malignant transformation
CANCER
©UWorld

(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA

©UWorld

Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two types of genes

Exhibit Display

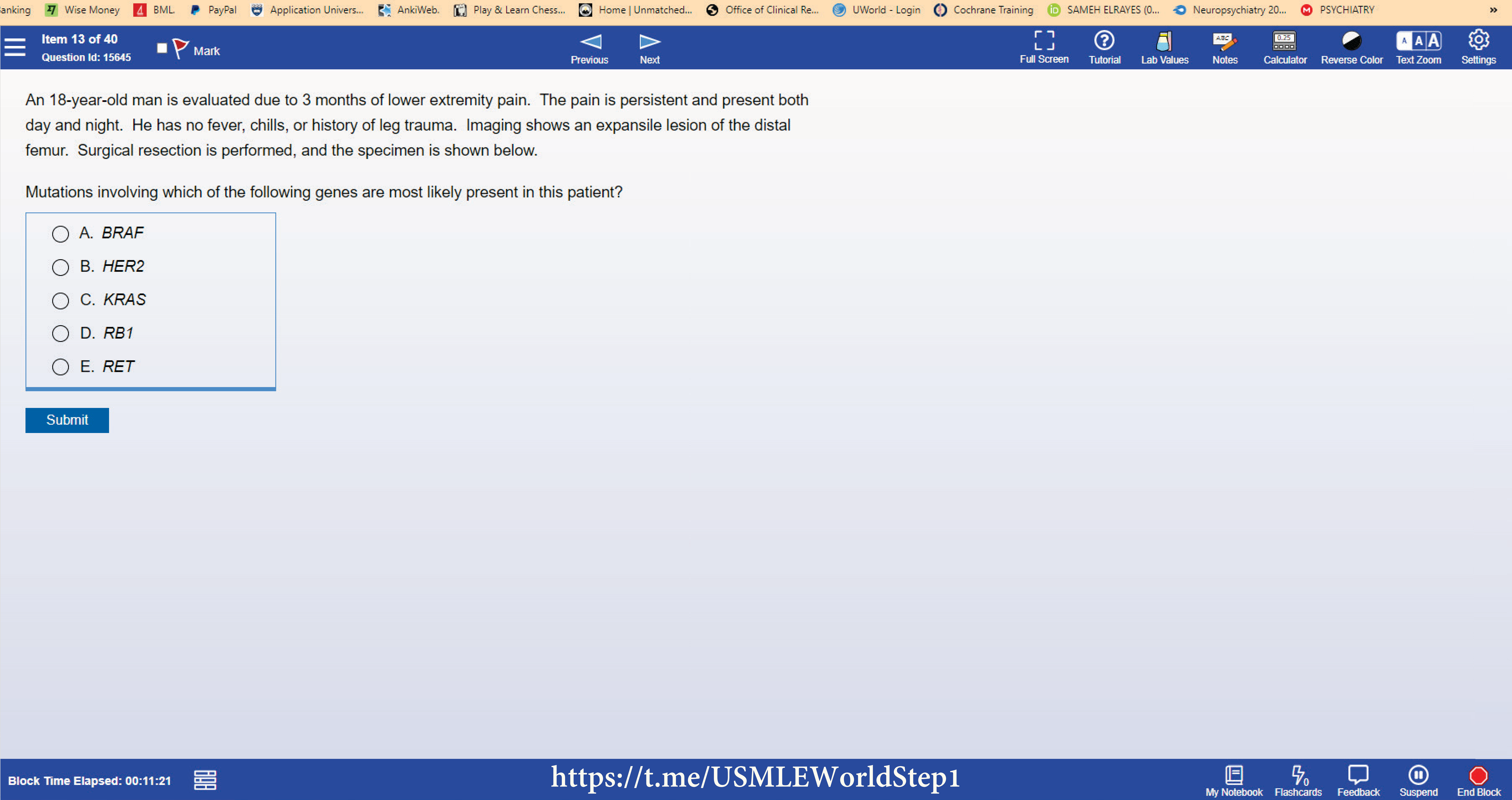


Oncogenes versus tumor suppressor genes

Proto-oncogene
Tumor suppressor gene
Oncogene (activating mutation in at least 1 allele)
Inactivating mutation in both alleles
Controlled cell growth
Uncontrolled cell growth
©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA

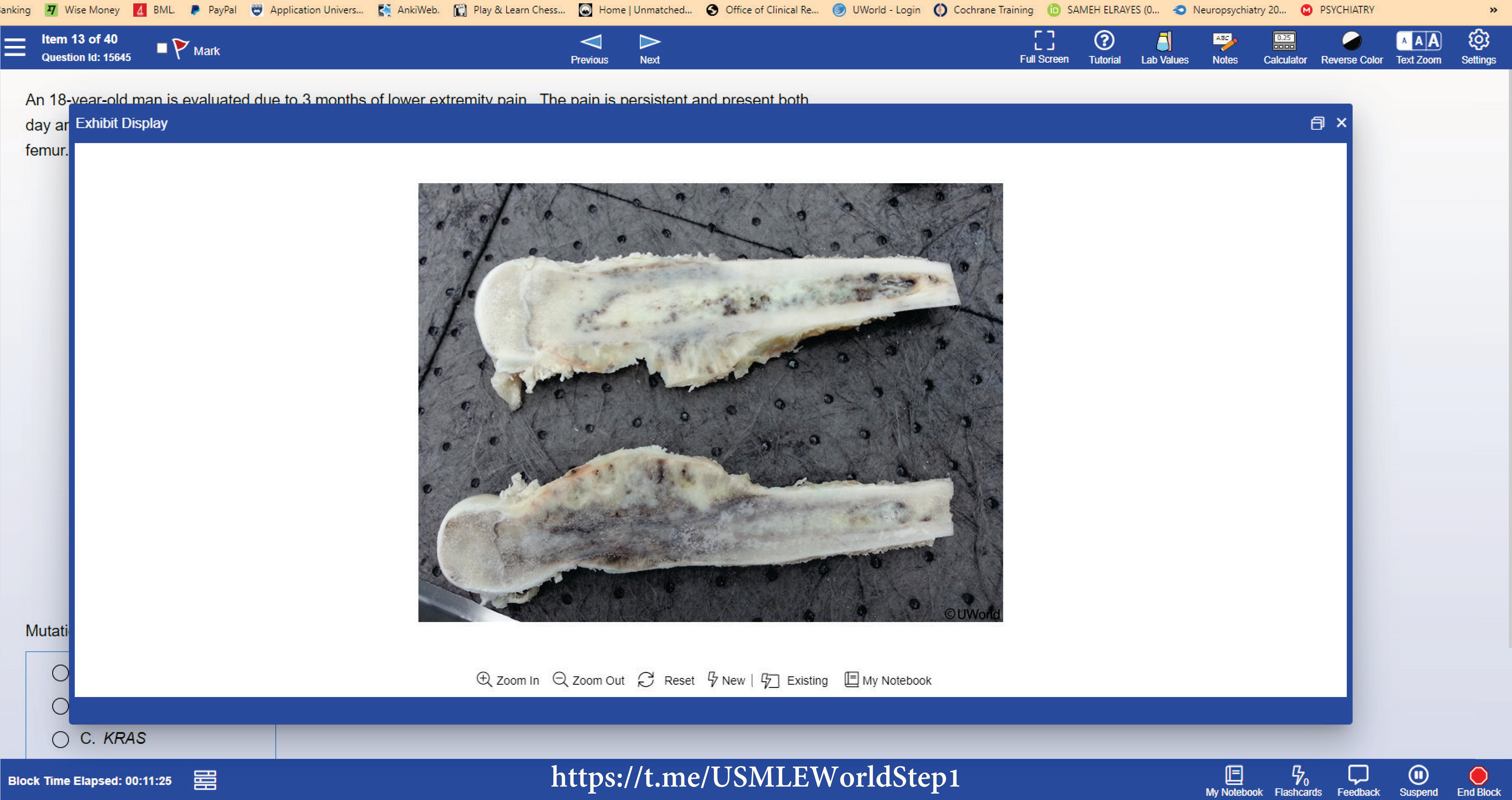

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

An 18-year-old man is evaluated due to 3 months of lower extremity pain. The pain is persistent and present both day and night. He has no fever, chills, or history of leg trauma. Imaging shows an expansile lesion of the distal femur. Surgical resection is performed, and the specimen is shown below.

Mutations involving which of the following genes are most likely present in this patient?

○ A. *BRAF*
○ B. *HER2*
○ C. *KRAS*
○ D. *RB1*
○ E. *RET*

Submit
Block Time Elapsed: 00:11:21
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:25
My Notebook
Flashcards
Feedback
Suspend
End Block

An 18-year-old man is evaluated due to 3 months of lower extremity pain. The pain is persistent and present both

day ar

femur.

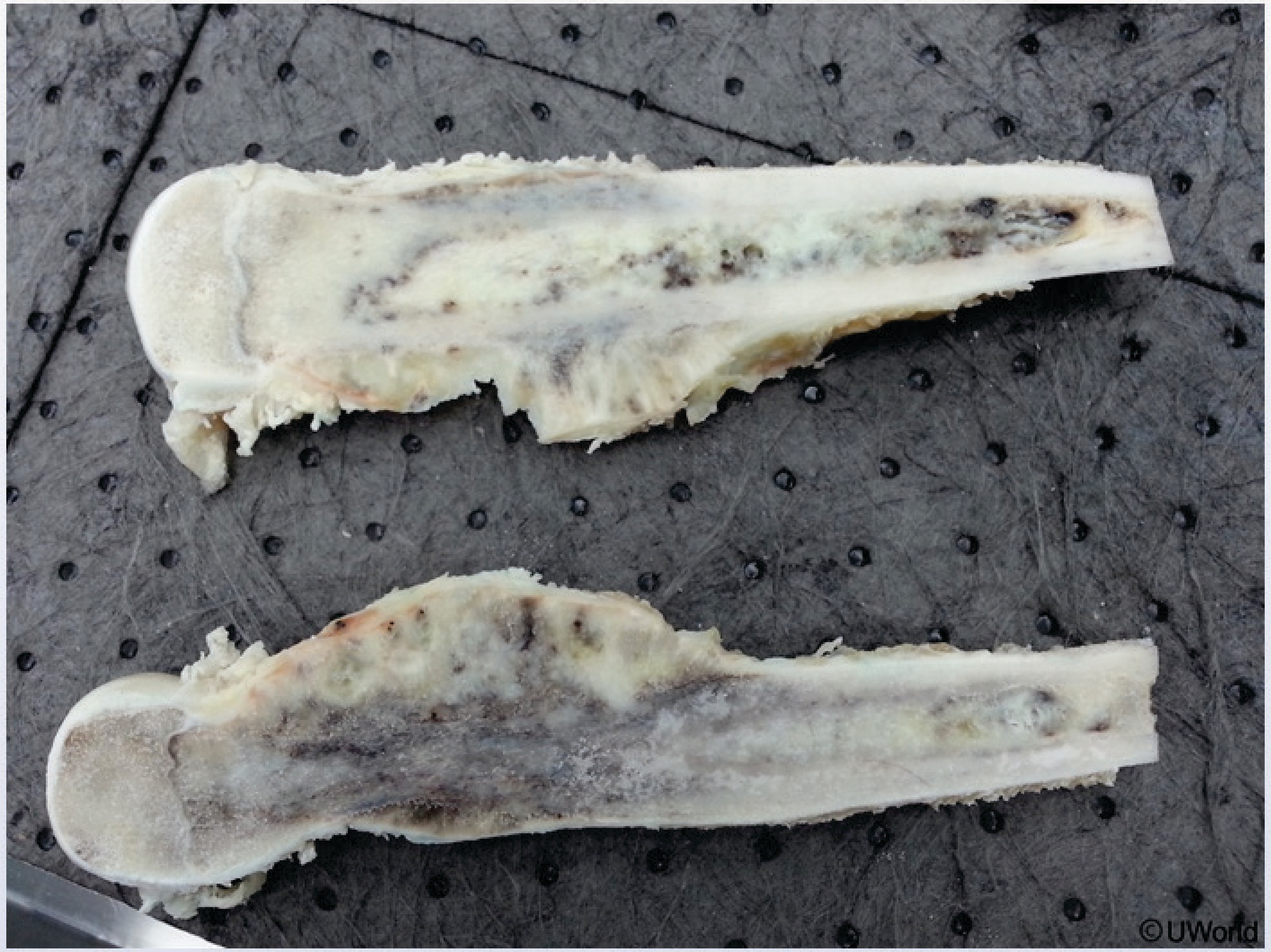
Mutati

○

○

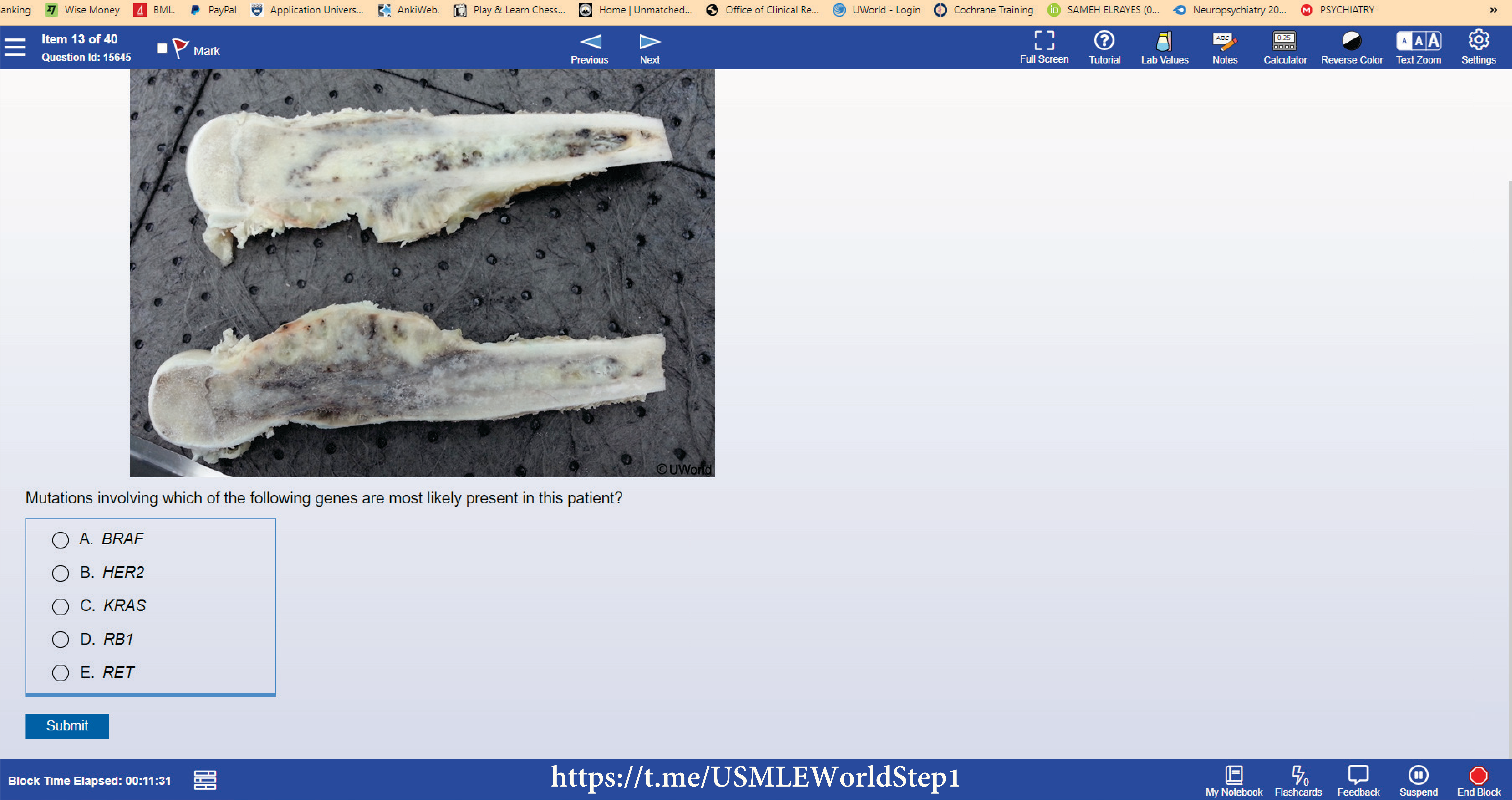
○ C. *KRAS*

An 18-year-old man is evaluated due to 3 months of lower extremity pain. The pain is persistent and present both day and night. He has no fever, chills, or history of leg trauma. Imaging shows an expansile lesion of the distal femur. Surgical resection is performed, and the specimen is shown below.


©UWorld

Mutations involving which of the following genes are most likely present in this patient?

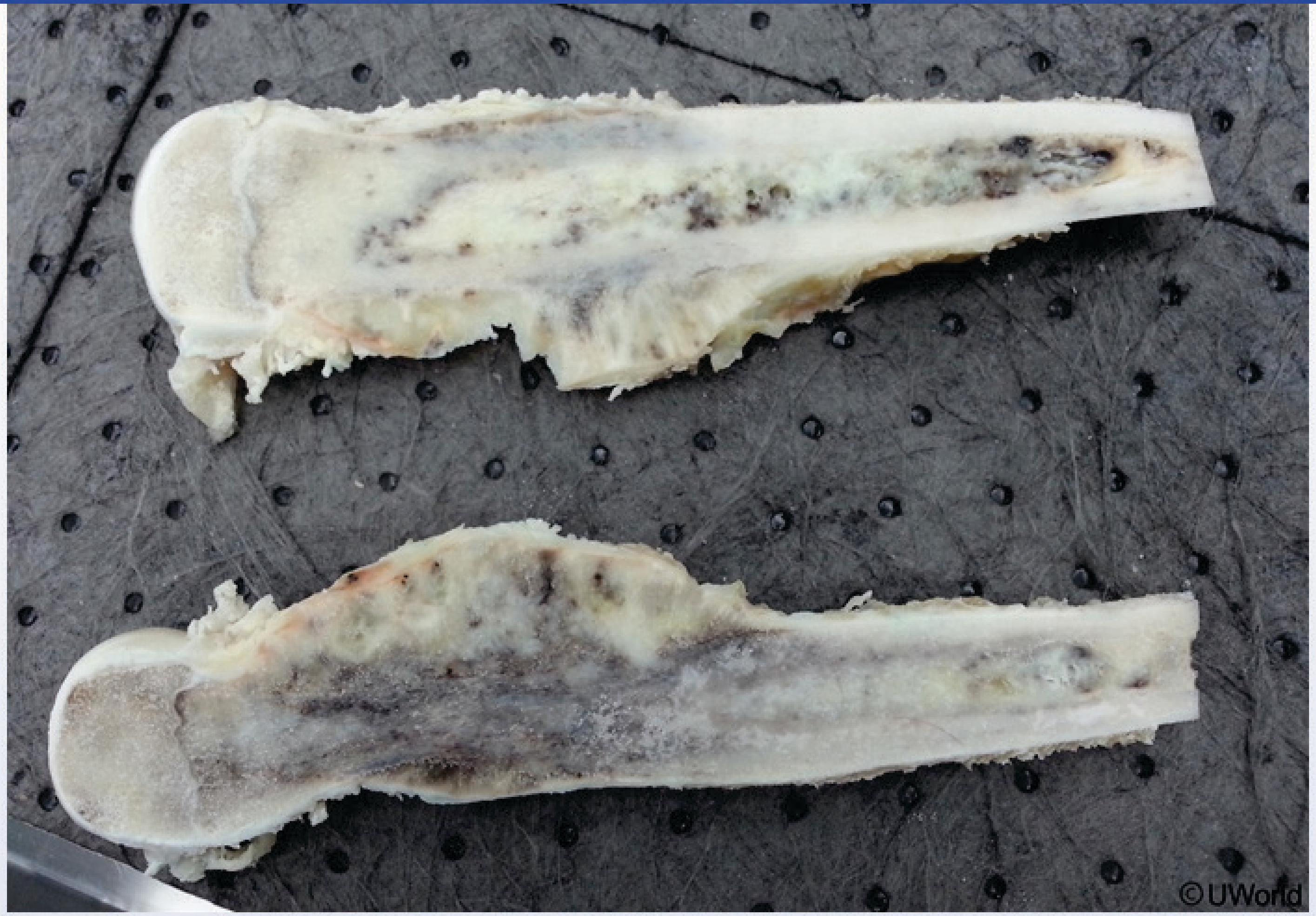
○ A. *BRAF*
○ B. *HER2*
○ C. *KRAS*


Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Block Time Elapsed: 00:11:31
My Notebook
Flashcards
Feedback
Suspend
End Block

Mutations involving which of the following genes are most likely present in this patient?

○ A. *BRAF*
○ B. *HER2*
○ C. *KRAS*
○ D. *RB1*
○ E. *RET*

Submit



Mutations involving which of the following genes are most likely present in this patient?

○ A. *BRAF* (9%)

✗ ● B. *HER2* (0%)

○ C. *KRAS* (9%)

✓ ○ D. *RB1* (71%)

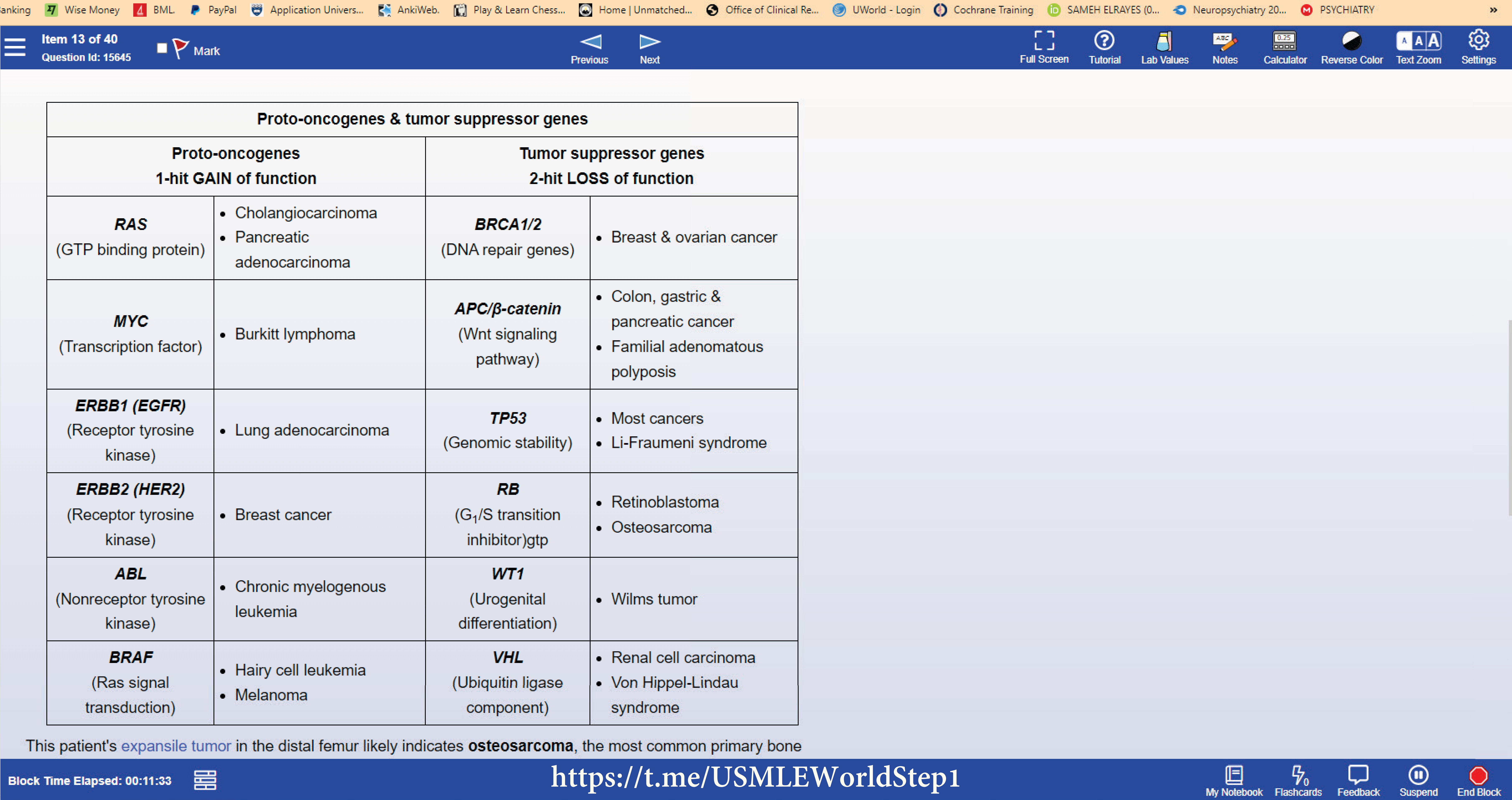
○ E. *RET* (8%)

Incorrect
Correct answer
D

71%
Answered correctly

13 secs
Time Spent

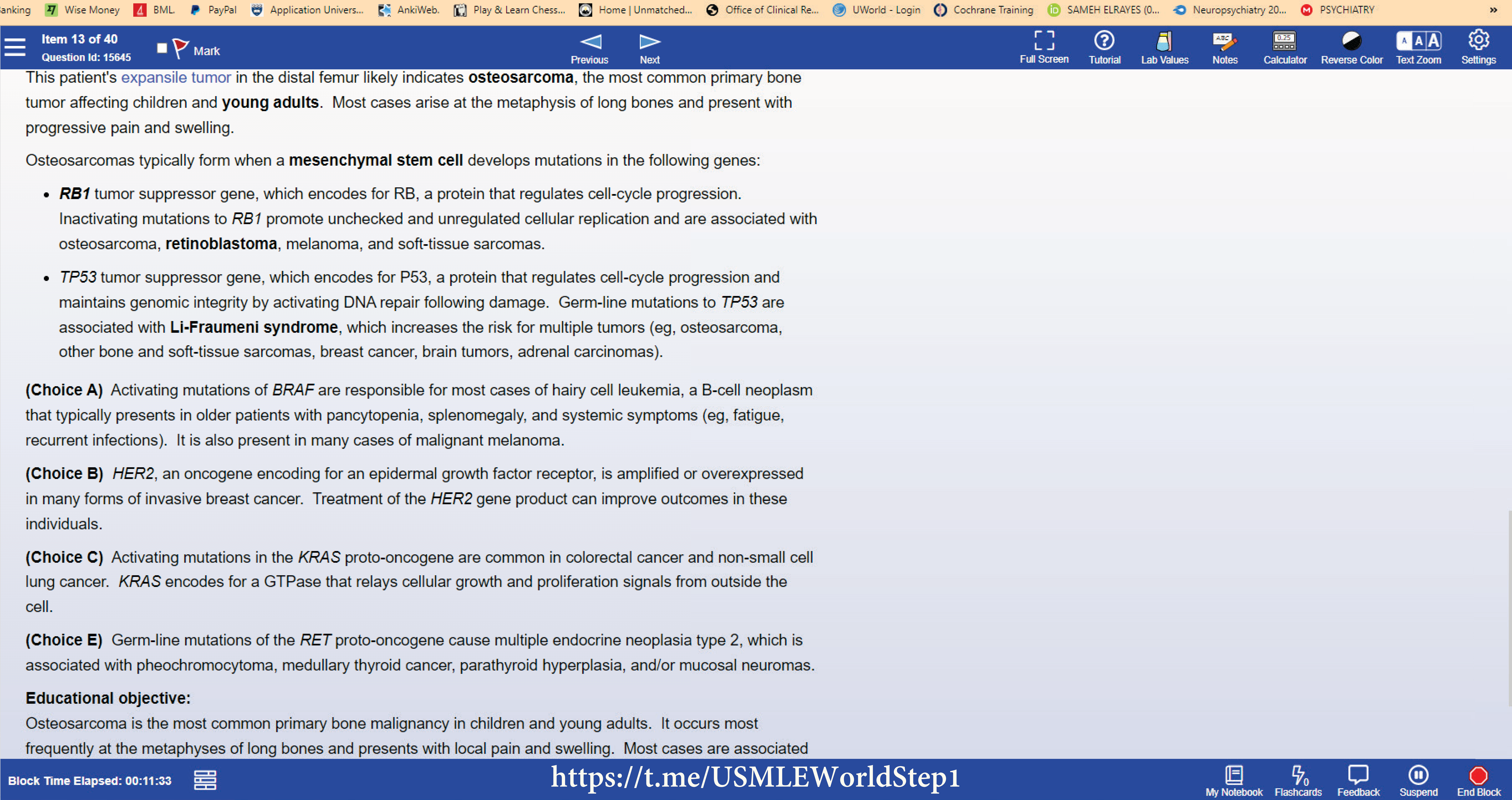
2023
Version


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:33
My Notebook
Flashcards
Feedback
Suspend
End Block

Proto-oncogenes & tumor suppressor genes

Proto-oncogenes 1-hit GAIN of function		**Tumor suppressor genes 2-hit LOSS of function**	
RAS (GTP binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	• Breast & ovarian cancer
MYC (Transcription factor)	• Burkitt lymphoma	***APC/β-catenin*** (Wnt signaling pathway)	• Colon, gastric & pancreatic cancer • Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	***TP53*** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)gtp	• Retinoblastoma • Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	• Chronic myelogenous leukemia	***WT1*** (Urogenital differentiation)	• Wilms tumor
BRAF (Ras signal transduction)	• Hairy cell leukemia • Melanoma	***VHL*** (Ubiquitin ligase component)	• Renal cell carcinoma • Von Hippel-Lindau syndrome

This patient's expansile tumor in the distal femur likely indicates **osteosarcoma**, the most common primary bone


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:33
https://t.me/USMLEWorldStep1
My Notebook
Flashcards
Feedback
Suspend
End Block

This patient's expansile tumor in the distal femur likely indicates **osteosarcoma**, the most common primary bone tumor affecting children and **young adults**. Most cases arise at the metaphysis of long bones and present with progressive pain and swelling.

Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression. Inactivating mutations to *RB1* promote unchecked and unregulated cellular replication and are associated with osteosarcoma, **retinoblastoma**, melanoma, and soft-tissue sarcomas.
- *TP53* tumor suppressor gene, which encodes for P53, a protein that regulates cell-cycle progression and maintains genomic integrity by activating DNA repair following damage. Germ-line mutations to *TP53* are associated with **Li-Fraumeni syndrome**, which increases the risk for multiple tumors (eg, osteosarcoma, other bone and soft-tissue sarcomas, breast cancer, brain tumors, adrenal carcinomas).

(Choice A) Activating mutations of *BRAF* are responsible for most cases of hairy cell leukemia, a B-cell neoplasm that typically presents in older patients with pancytopenia, splenomegaly, and systemic symptoms (eg, fatigue, recurrent infections). It is also present in many cases of malignant melanoma.

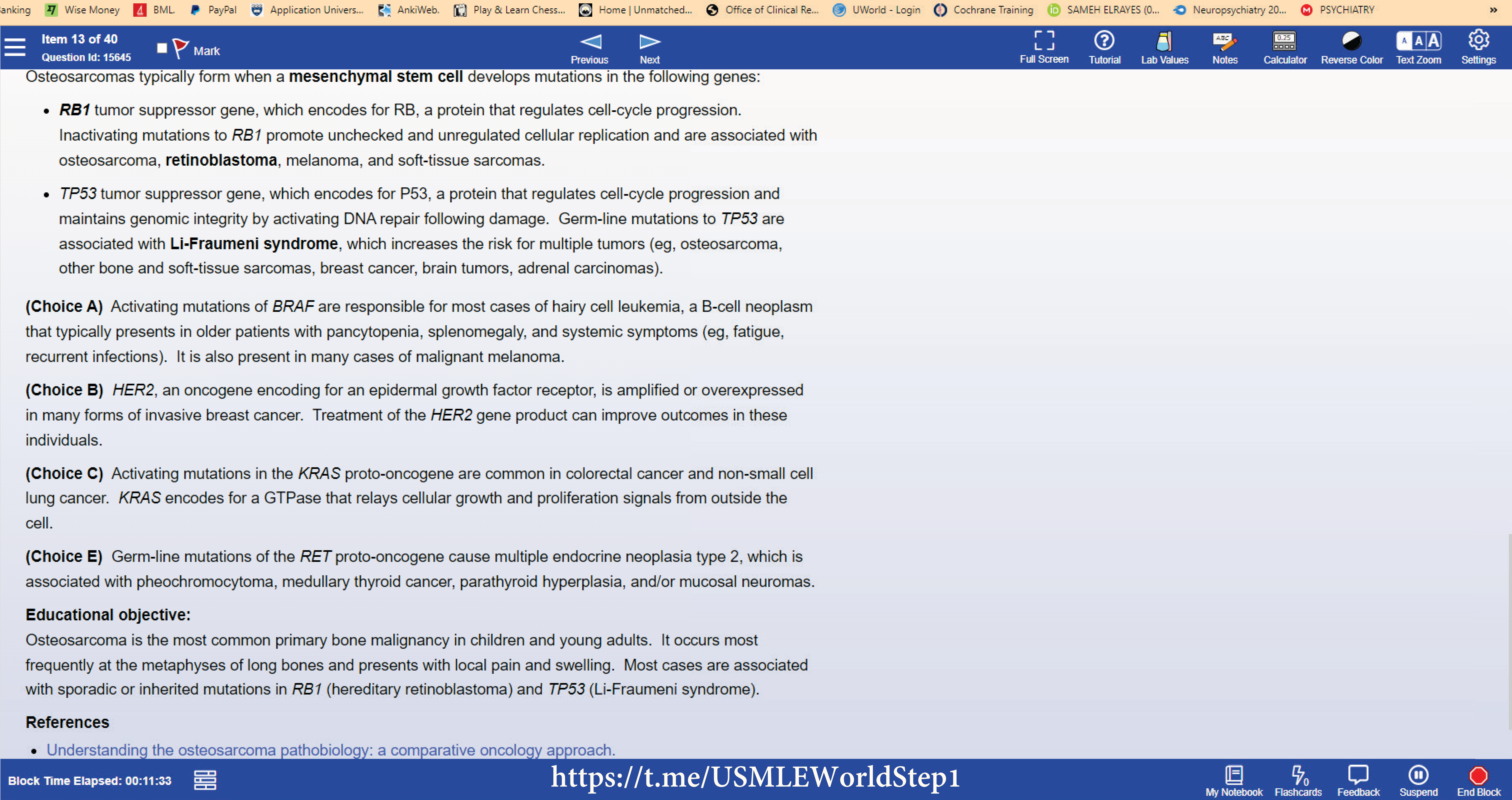
(Choice B) *HER2*, an oncogene encoding for an epidermal growth factor receptor, is amplified or overexpressed in many forms of invasive breast cancer. Treatment of the *HER2* gene product can improve outcomes in these individuals.

(Choice C) Activating mutations in the *KRAS* proto-oncogene are common in colorectal cancer and non-small cell lung cancer. *KRAS* encodes for a GTPase that relays cellular growth and proliferation signals from outside the cell.

(Choice E) Germ-line mutations of the *RET* proto-oncogene cause multiple endocrine neoplasia type 2, which is associated with pheochromocytoma, medullary thyroid cancer, parathyroid hyperplasia, and/or mucosal neuromas.

Educational objective:

Osteosarcoma is the most common primary bone malignancy in children and young adults. It occurs most frequently at the metaphyses of long bones and presents with local pain and swelling. Most cases are associated


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 13 of 40
Question Id: 15645
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression. Inactivating mutations to *RB1* promote unchecked and unregulated cellular replication and are associated with osteosarcoma, **retinoblastoma**, melanoma, and soft-tissue sarcomas.
- *TP53* tumor suppressor gene, which encodes for P53, a protein that regulates cell-cycle progression and maintains genomic integrity by activating DNA repair following damage. Germ-line mutations to *TP53* are associated with **Li-Fraumeni syndrome**, which increases the risk for multiple tumors (eg, osteosarcoma, other bone and soft-tissue sarcomas, breast cancer, brain tumors, adrenal carcinomas).

(Choice A) Activating mutations of *BRAF* are responsible for most cases of hairy cell leukemia, a B-cell neoplasm that typically presents in older patients with pancytopenia, splenomegaly, and systemic symptoms (eg, fatigue, recurrent infections). It is also present in many cases of malignant melanoma.

(Choice B) *HER2*, an oncogene encoding for an epidermal growth factor receptor, is amplified or overexpressed in many forms of invasive breast cancer. Treatment of the *HER2* gene product can improve outcomes in these individuals.

(Choice C) Activating mutations in the *KRAS* proto-oncogene are common in colorectal cancer and non-small cell lung cancer. *KRAS* encodes for a GTPase that relays cellular growth and proliferation signals from outside the cell.

(Choice E) Germ-line mutations of the *RET* proto-oncogene cause multiple endocrine neoplasia type 2, which is associated with pheochromocytoma, medullary thyroid cancer, parathyroid hyperplasia, and/or mucosal neuromas.

Educational objective:

Osteosarcoma is the most common primary bone malignancy in children and young adults. It occurs most frequently at the metaphyses of long bones and presents with local pain and swelling. Most cases are associated with sporadic or inherited mutations in *RB1* (hereditary retinoblastoma) and *TP53* (Li-Fraumeni syndrome).

References

- Understanding the osteosarcoma pathobiology: a comparative oncology approach.

Block Time Elapsed: 00:11:33
My Notebook
Flashcards
Feedback
Suspend
End Block

ABL

(Nonreceptor tyrosine

- Chronic myelogenous

WT1

(Urogenital

- Wilms tumor

This p

tumor

progre

Osteo

- R

  Ir

  o

- T

  m

  a

  o

(Choi

that ty

recurr

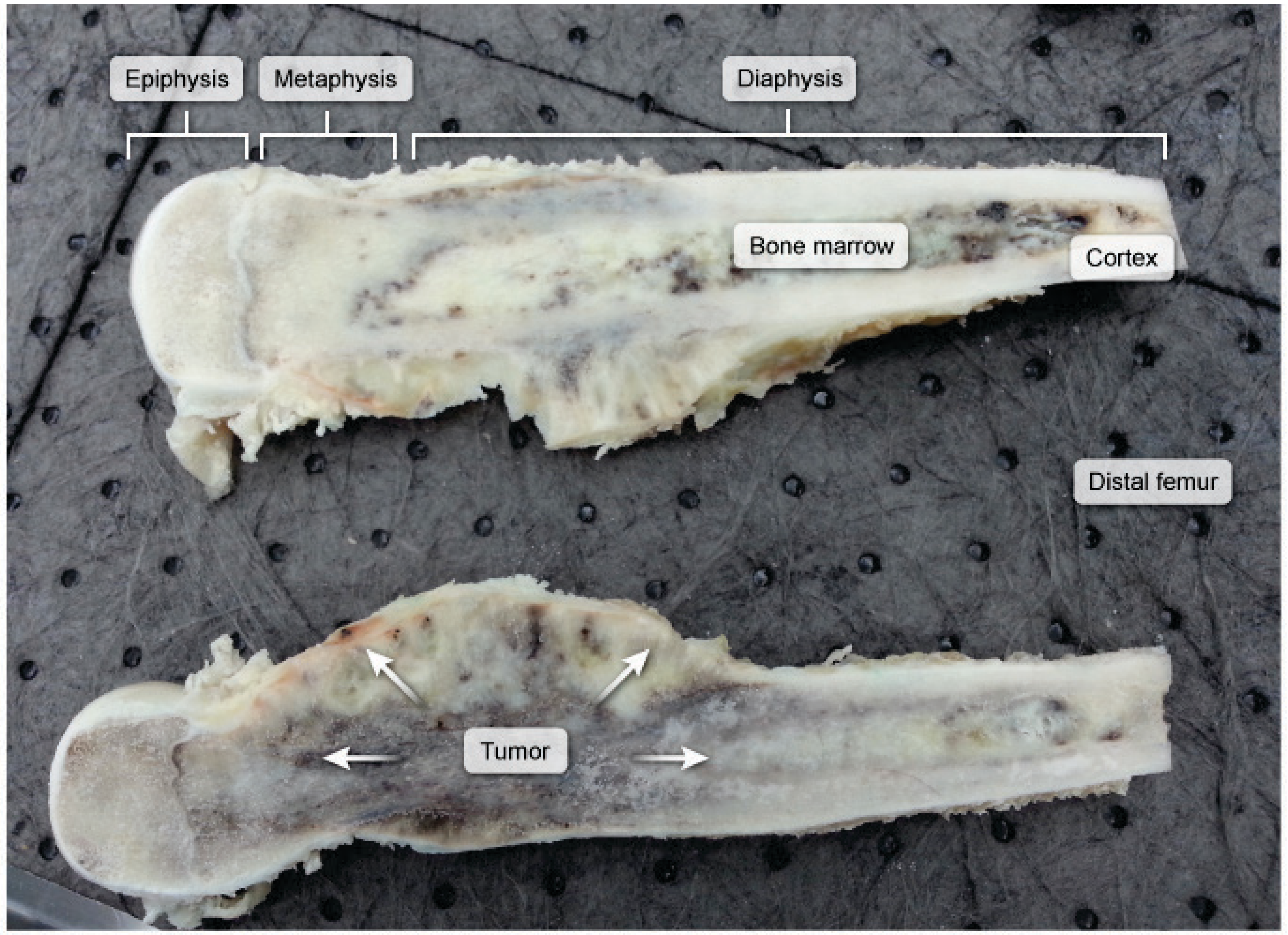
(Choi

in mar

individ

Exhibit Display

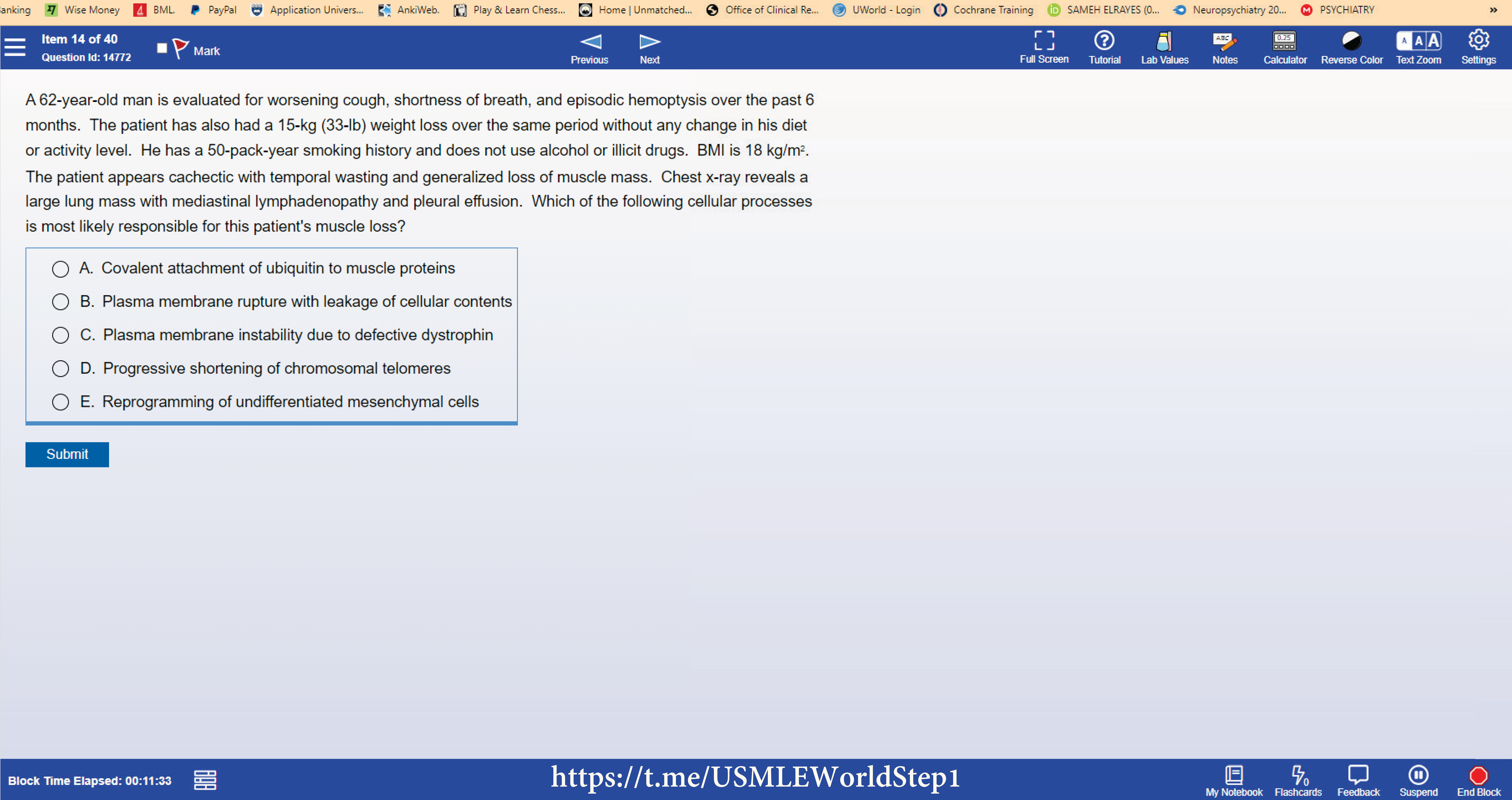
Osteosarcoma



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

(Choice C) Activating mutations in the *KRAS* proto-oncogene are common in colorectal cancer and non-small cell lung cancer. *KRAS* encodes for a GTPase that relays cellular growth and proliferation signals from outside the


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 14 of 40
Question Id: 14772
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:33
My Notebook
Flashcards
Feedback
Suspend
End Block

A 62-year-old man is evaluated for worsening cough, shortness of breath, and episodic hemoptysis over the past 6 months. The patient has also had a 15-kg (33-lb) weight loss over the same period without any change in his diet or activity level. He has a 50-pack-year smoking history and does not use alcohol or illicit drugs. BMI is 18 kg/m². The patient appears cachectic with temporal wasting and generalized loss of muscle mass. Chest x-ray reveals a large lung mass with mediastinal lymphadenopathy and pleural effusion. Which of the following cellular processes is most likely responsible for this patient's muscle loss?

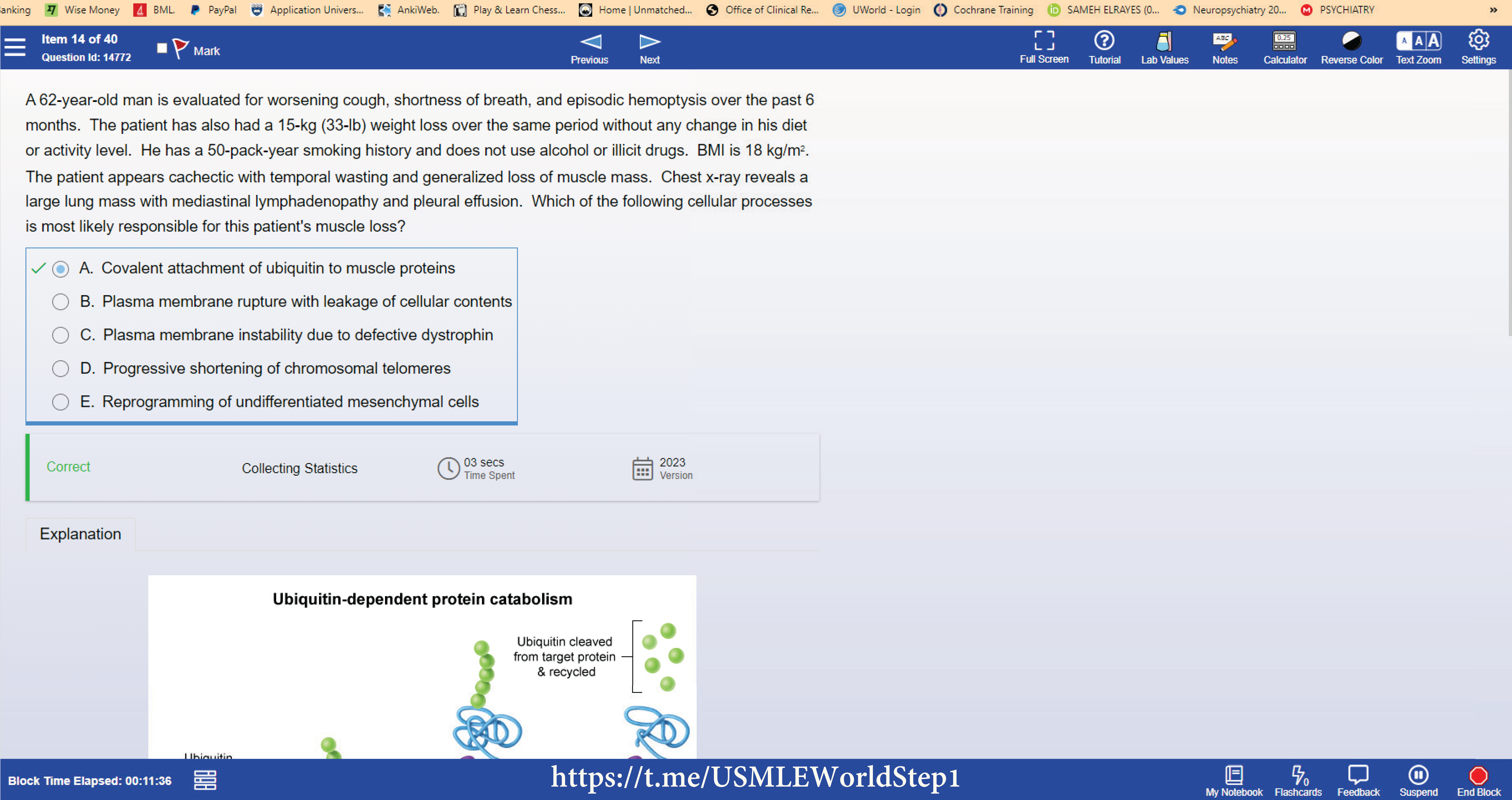
○ A. Covalent attachment of ubiquitin to muscle proteins

○ B. Plasma membrane rupture with leakage of cellular contents

○ C. Plasma membrane instability due to defective dystrophin

○ D. Progressive shortening of chromosomal telomeres

○ E. Reprogramming of undifferentiated mesenchymal cells


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 14 of 40
Question Id: 14772
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 62-year-old man is evaluated for worsening cough, shortness of breath, and episodic hemoptysis over the past 6 months. The patient has also had a 15-kg (33-lb) weight loss over the same period without any change in his diet or activity level. He has a 50-pack-year smoking history and does not use alcohol or illicit drugs. BMI is 18 kg/m². The patient appears cachectic with temporal wasting and generalized loss of muscle mass. Chest x-ray reveals a large lung mass with mediastinal lymphadenopathy and pleural effusion. Which of the following cellular processes is most likely responsible for this patient's muscle loss?

✓ ● A. Covalent attachment of ubiquitin to muscle proteins

○ B. Plasma membrane rupture with leakage of cellular contents

○ C. Plasma membrane instability due to defective dystrophin

○ D. Progressive shortening of chromosomal telomeres

○ E. Reprogramming of undifferentiated mesenchymal cells

Correct | Collecting Statistics | 03 secs Time Spent | 2023 Version

Explanation

Ubiquitin-dependent protein catabolism

Ubiquitin cleaved from target protein & recycled
Ubiquitin

Block Time Elapsed: 00:11:36

My Notebook
Flashcards
Feedback
Suspend
End Block

anking Wise Money BML PayPal Application Univers... AnkiWeb. Play & Learn Chess... Home | Unmatched... Office of Clinical Re... UWorld - Login Cochrane Training SAMEH ELRAYES (0... Neuropsychiatry 20... PSYCHIATRY

Item 14 of 40
Question Id: 14772

☐ Mark

Previous Next

Full Screen Tutorial Lab Values Notes Calculator Reverse Color Text Zoom Settings

A 62-year-old man is evaluated for worsening cough, shortness of breath, and episodic hemoptysis over the past 6

month

or acti

The pa

large l

is mos

✓ ●

○

○

○

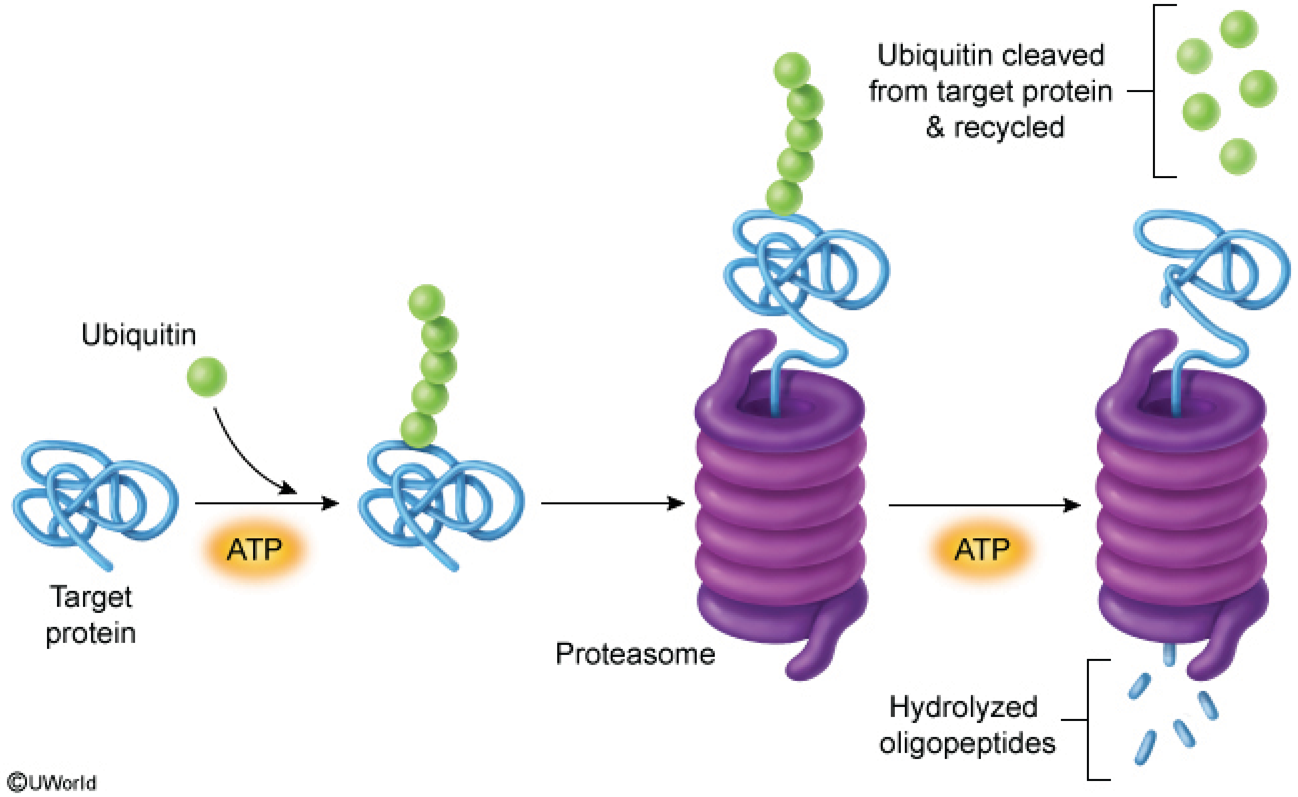
○

Cor

Expl

Exhibit Display

Ubiquitin-dependent protein catabolism



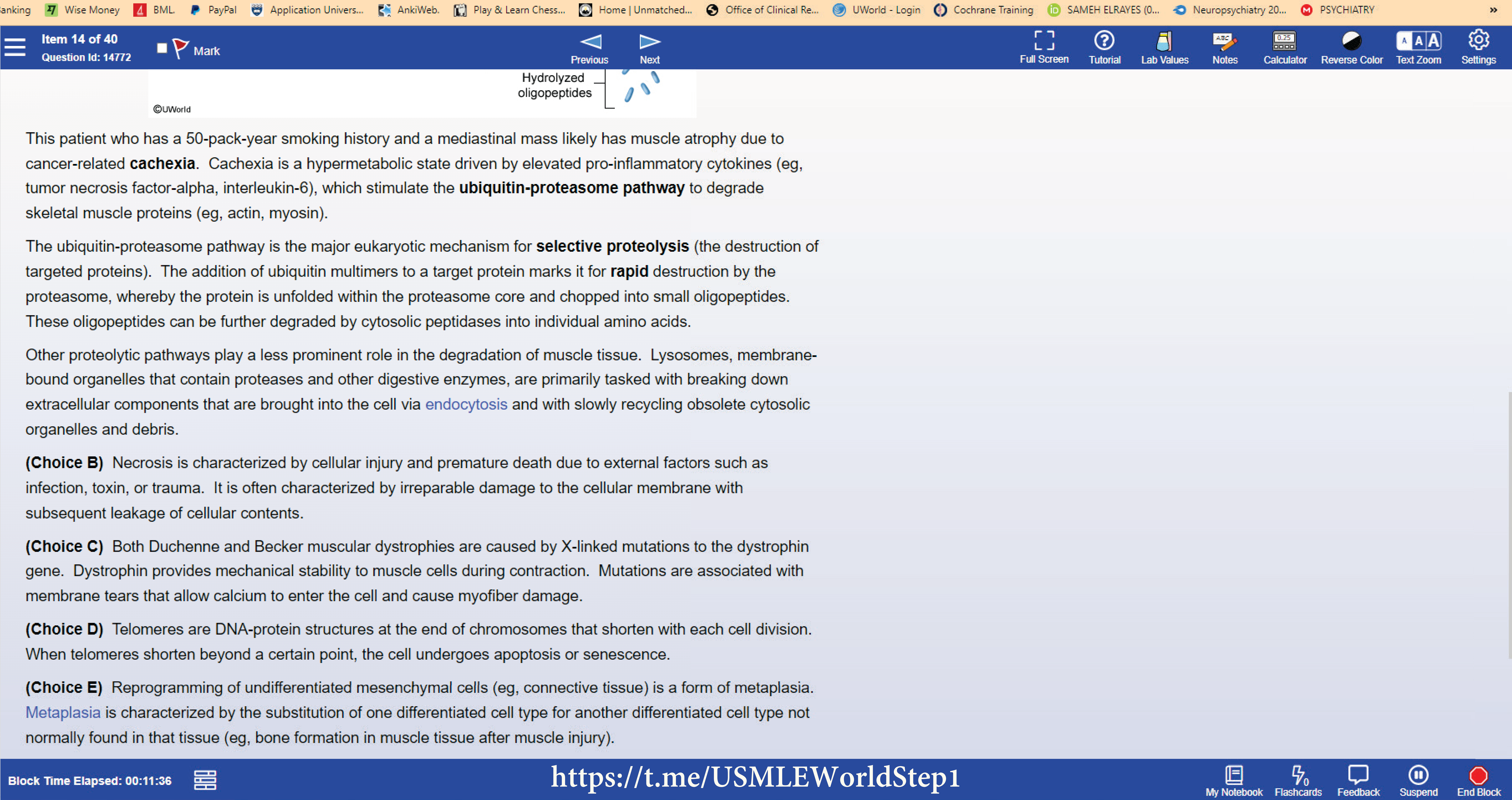
Ubiquitin cleaved from target protein & recycled
Ubiquitin
ATP
Target protein
Proteasome
ATP
Hydrolyzed oligopeptides
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Block Time Elapsed: 00:11:36

https://t.me/USMLEWorldStep1

My Notebook Flashcards Feedback Suspend End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Hydrolyzed oligopeptides
©UWorld
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 14 of 40
Question Id: 14772

This patient who has a 50-pack-year smoking history and a mediastinal mass likely has muscle atrophy due to cancer-related **cachexia**. Cachexia is a hypermetabolic state driven by elevated pro-inflammatory cytokines (eg, tumor necrosis factor-alpha, interleukin-6), which stimulate the **ubiquitin-proteasome pathway** to degrade skeletal muscle proteins (eg, actin, myosin).

The ubiquitin-proteasome pathway is the major eukaryotic mechanism for **selective proteolysis** (the destruction of targeted proteins). The addition of ubiquitin multimers to a target protein marks it for **rapid** destruction by the proteasome, whereby the protein is unfolded within the proteasome core and chopped into small oligopeptides. These oligopeptides can be further degraded by cytosolic peptidases into individual amino acids.

Other proteolytic pathways play a less prominent role in the degradation of muscle tissue. Lysosomes, membrane-bound organelles that contain proteases and other digestive enzymes, are primarily tasked with breaking down extracellular components that are brought into the cell via endocytosis and with slowly recycling obsolete cytosolic organelles and debris.

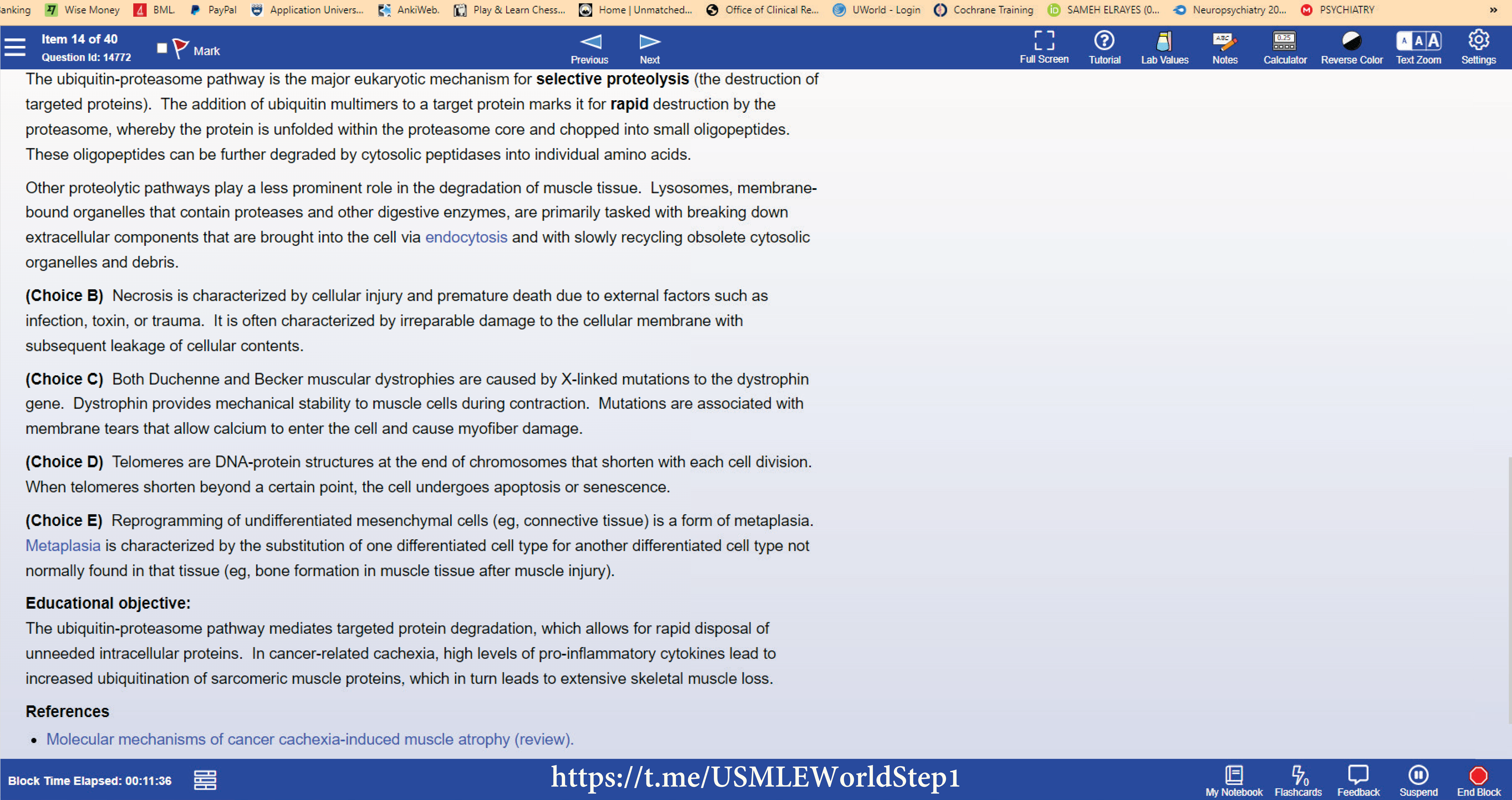
(Choice B) Necrosis is characterized by cellular injury and premature death due to external factors such as infection, toxin, or trauma. It is often characterized by irreparable damage to the cellular membrane with subsequent leakage of cellular contents.

(Choice C) Both Duchenne and Becker muscular dystrophies are caused by X-linked mutations to the dystrophin gene. Dystrophin provides mechanical stability to muscle cells during contraction. Mutations are associated with membrane tears that allow calcium to enter the cell and cause myofiber damage.

(Choice D) Telomeres are DNA-protein structures at the end of chromosomes that shorten with each cell division. When telomeres shorten beyond a certain point, the cell undergoes apoptosis or senescence.

(Choice E) Reprogramming of undifferentiated mesenchymal cells (eg, connective tissue) is a form of metaplasia. Metaplasia is characterized by the substitution of one differentiated cell type for another differentiated cell type not normally found in that tissue (eg, bone formation in muscle tissue after muscle injury).

Block Time Elapsed: 00:11:36


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 14 of 40
Question Id: 14772
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

The ubiquitin-proteasome pathway is the major eukaryotic mechanism for **selective proteolysis** (the destruction of targeted proteins). The addition of ubiquitin multimers to a target protein marks it for **rapid** destruction by the proteasome, whereby the protein is unfolded within the proteasome core and chopped into small oligopeptides. These oligopeptides can be further degraded by cytosolic peptidases into individual amino acids.

Other proteolytic pathways play a less prominent role in the degradation of muscle tissue. Lysosomes, membrane-bound organelles that contain proteases and other digestive enzymes, are primarily tasked with breaking down extracellular components that are brought into the cell via endocytosis and with slowly recycling obsolete cytosolic organelles and debris.

(Choice B) Necrosis is characterized by cellular injury and premature death due to external factors such as infection, toxin, or trauma. It is often characterized by irreparable damage to the cellular membrane with subsequent leakage of cellular contents.

(Choice C) Both Duchenne and Becker muscular dystrophies are caused by X-linked mutations to the dystrophin gene. Dystrophin provides mechanical stability to muscle cells during contraction. Mutations are associated with membrane tears that allow calcium to enter the cell and cause myofiber damage.

(Choice D) Telomeres are DNA-protein structures at the end of chromosomes that shorten with each cell division. When telomeres shorten beyond a certain point, the cell undergoes apoptosis or senescence.

(Choice E) Reprogramming of undifferentiated mesenchymal cells (eg, connective tissue) is a form of metaplasia. Metaplasia is characterized by the substitution of one differentiated cell type for another differentiated cell type not normally found in that tissue (eg, bone formation in muscle tissue after muscle injury).

Educational objective:

The ubiquitin-proteasome pathway mediates targeted protein degradation, which allows for rapid disposal of unneeded intracellular proteins. In cancer-related cachexia, high levels of pro-inflammatory cytokines lead to increased ubiquitination of sarcomeric muscle proteins, which in turn leads to extensive skeletal muscle loss.

References

- Molecular mechanisms of cancer cachexia-induced muscle atrophy (review).

Block Time Elapsed: 00:11:36
My Notebook
Flashcards
Feedback
Suspend
End Block

Hydrolyzed
oligopeptides

This p
cancer
tumor
skeleta

The ub
targete
protea
These

Other
bound
extrac
organe

(Choic
infectio
subseq

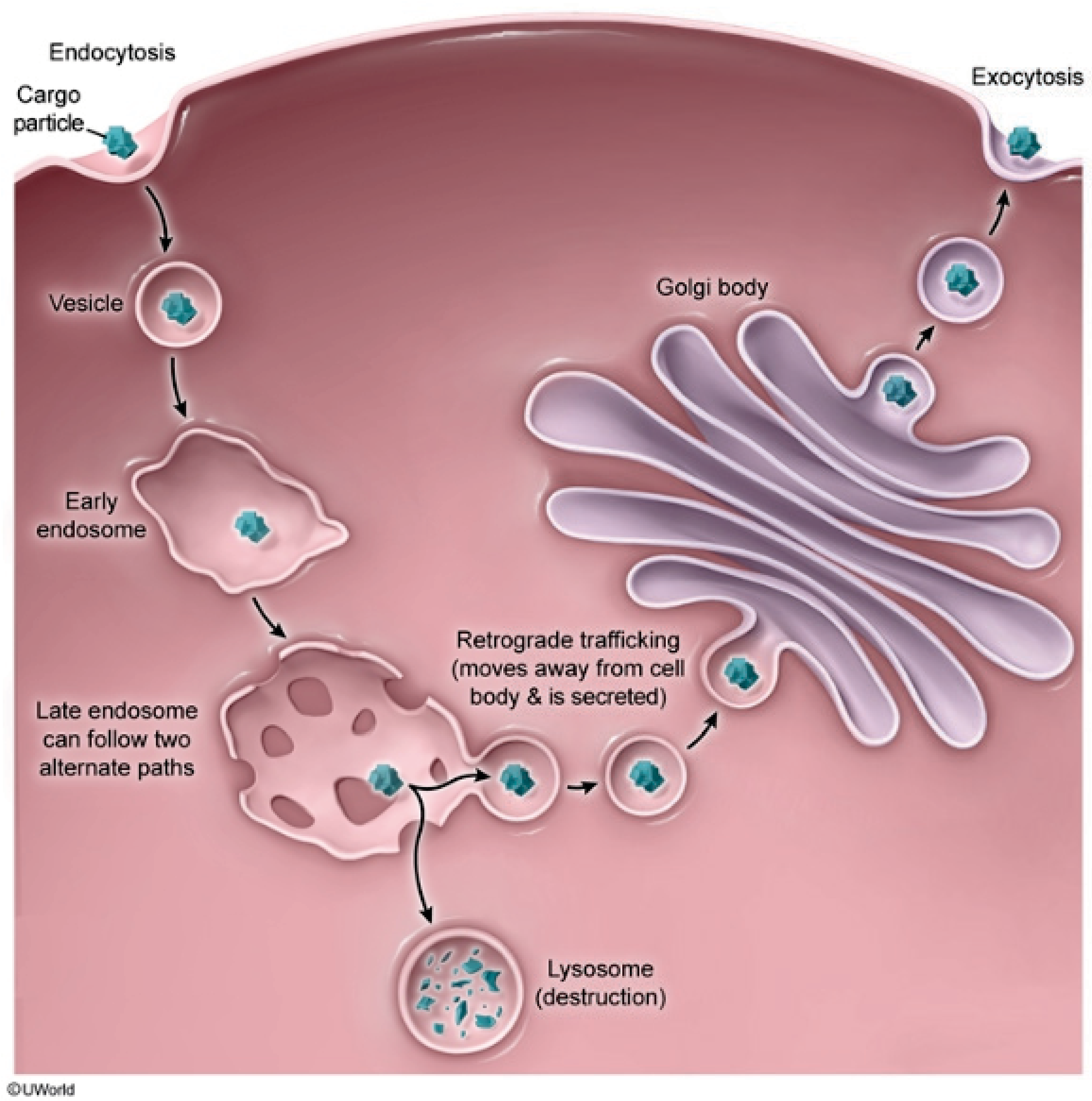
(Choic
gene.
memb

(Choic
When

(Choic
Metap

Exhibit Display

Endosomal pathway


Endocytosis
Cargo particle
Exocytosis
Vesicle
Golgi body
Early endosome
Retrograde trafficking (moves away from cell body & is secreted)
Late endosome can follow two alternate paths
Lysosome (destruction)
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

normally found in that tissue (eg, bone formation in muscle tissue after muscle injury).

The ubiquitin-proteasome pathway is the major eukaryotic mechanism for **selective proteolysis** (the destruction of targeted proteins). The addition of ubiquitin multimers to a target protein marks it for **rapid** destruction by the

protea

These

Other

bound

extrac

organe

(Choi

infecti

subse

(Choi

gene.

memb

(Choi

When

(Choi

Metap

norma

Educa

The ub

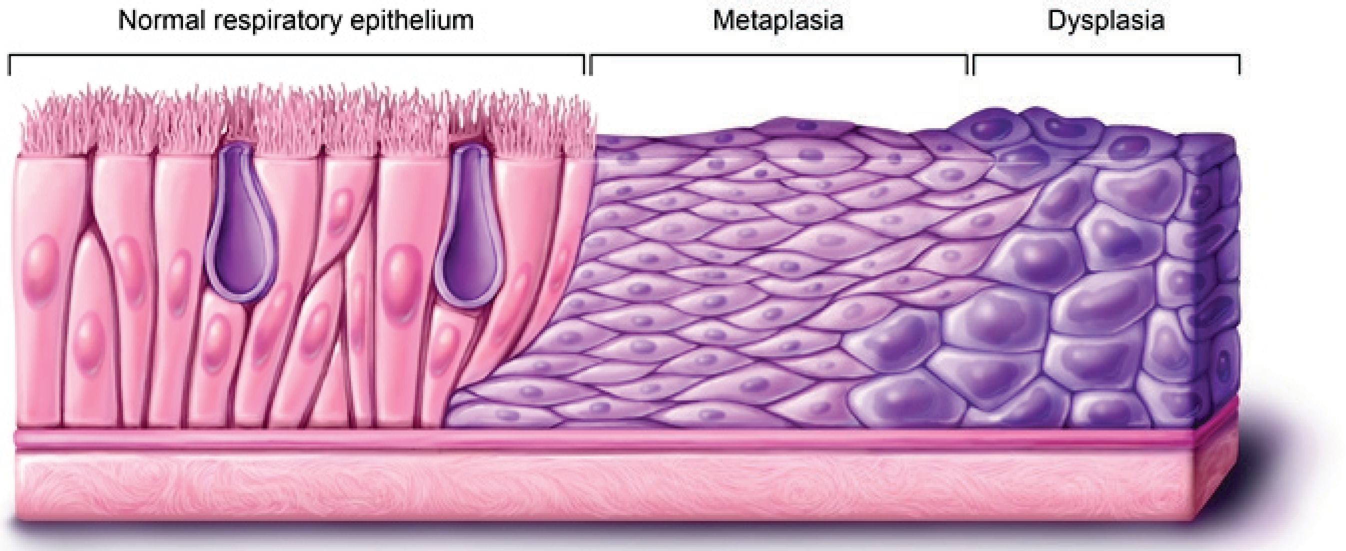
unnee

increa

Refere

Exhibit Display

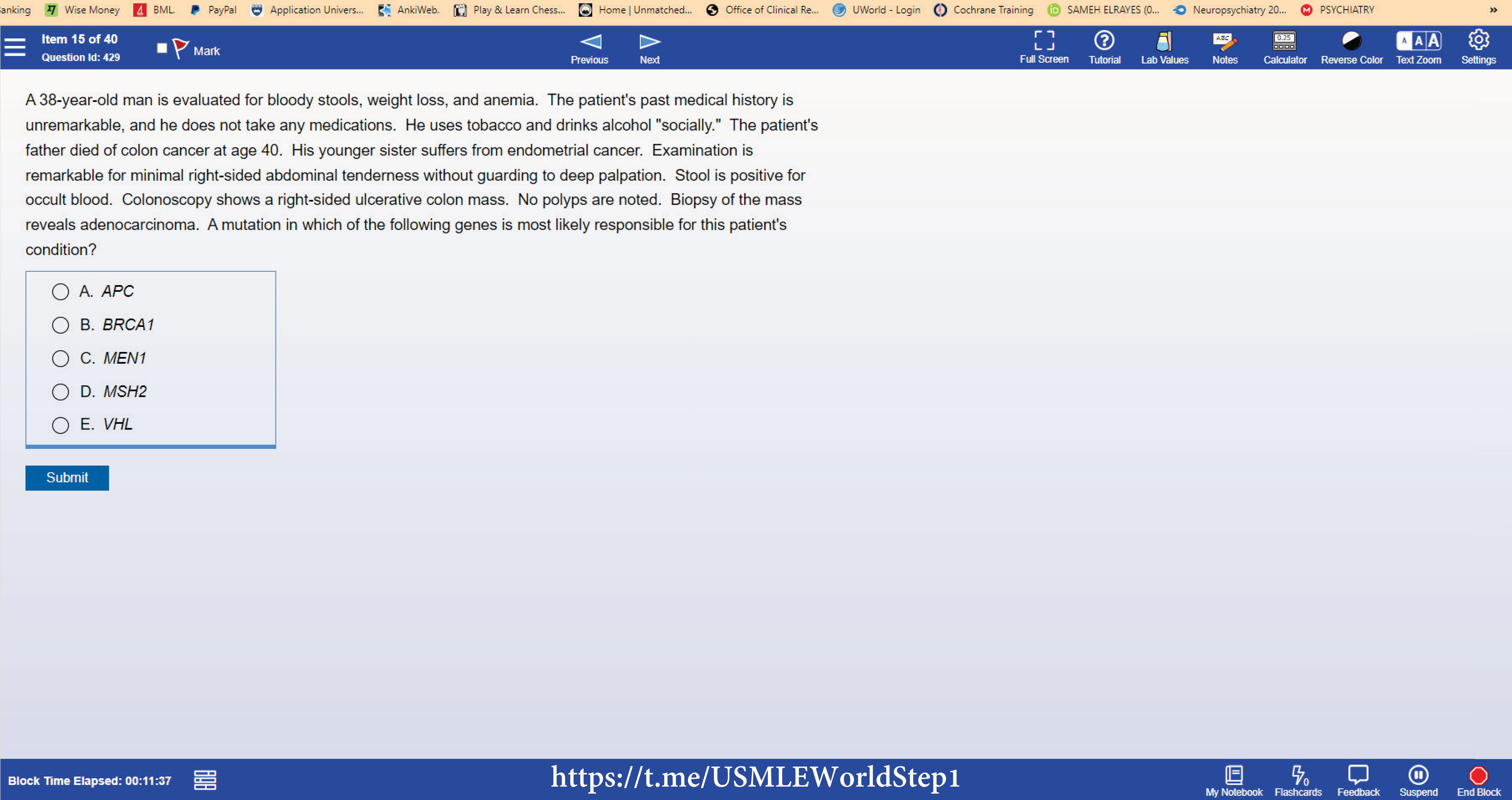
Squamous metaplasia



©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

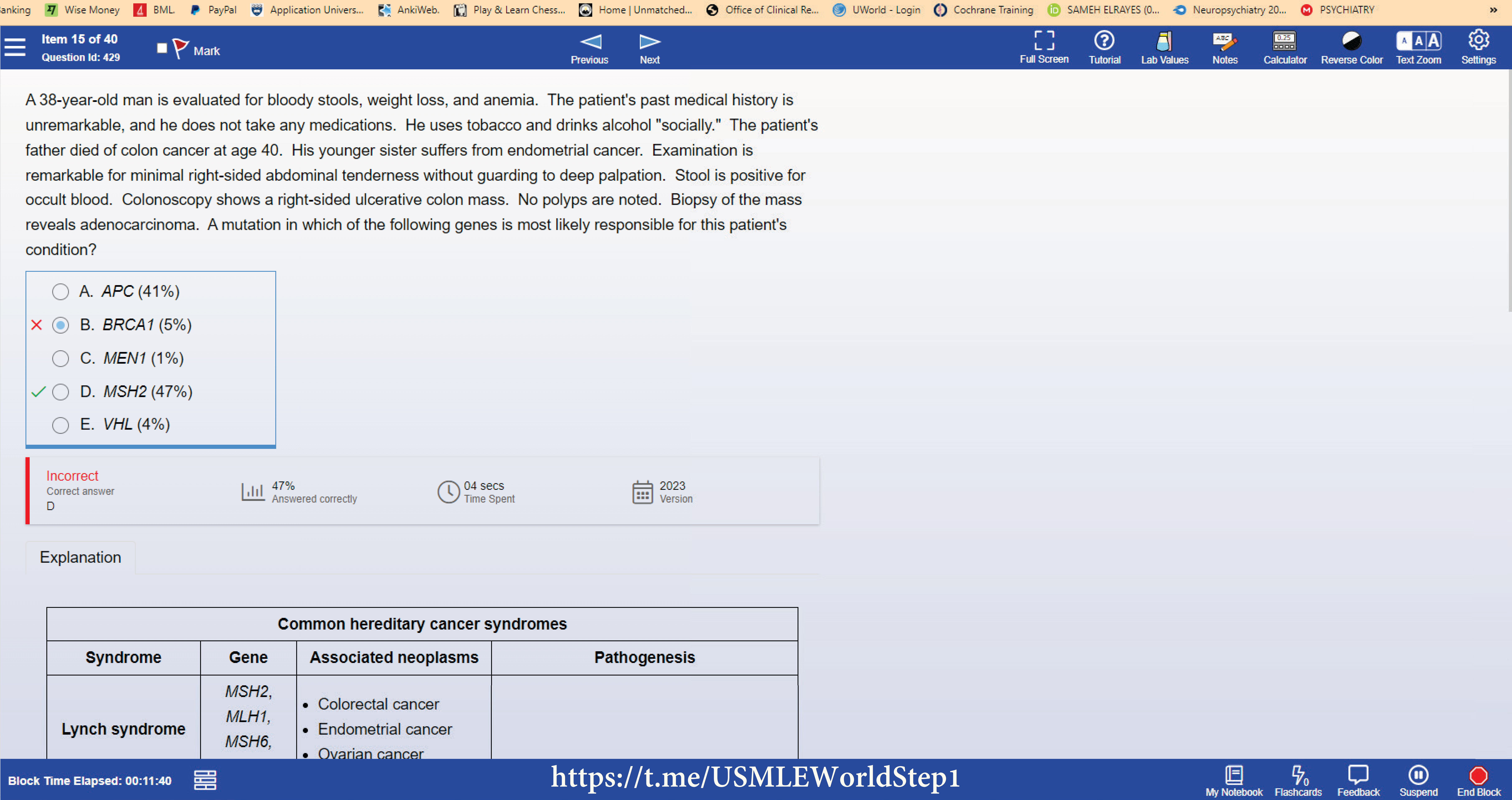
- Molecular mechanisms of cancer cachexia-induced muscle atrophy (review).


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 15 of 40
Question Id: 429
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 38-year-old man is evaluated for bloody stools, weight loss, and anemia. The patient's past medical history is unremarkable, and he does not take any medications. He uses tobacco and drinks alcohol "socially." The patient's father died of colon cancer at age 40. His younger sister suffers from endometrial cancer. Examination is remarkable for minimal right-sided abdominal tenderness without guarding to deep palpation. Stool is positive for occult blood. Colonoscopy shows a right-sided ulcerative colon mass. No polyps are noted. Biopsy of the mass reveals adenocarcinoma. A mutation in which of the following genes is most likely responsible for this patient's condition?

○ A. *APC*
○ B. *BRCA1*
○ C. *MEN1*
○ D. *MSH2*
○ E. *VHL*

Submit
Block Time Elapsed: 00:11:37
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 15 of 40
Question Id: 429
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 38-year-old man is evaluated for bloody stools, weight loss, and anemia. The patient's past medical history is unremarkable, and he does not take any medications. He uses tobacco and drinks alcohol "socially." The patient's father died of colon cancer at age 40. His younger sister suffers from endometrial cancer. Examination is remarkable for minimal right-sided abdominal tenderness without guarding to deep palpation. Stool is positive for occult blood. Colonoscopy shows a right-sided ulcerative colon mass. No polyps are noted. Biopsy of the mass reveals adenocarcinoma. A mutation in which of the following genes is most likely responsible for this patient's condition?

- ○ A. *APC* (41%)
- ✗ ● B. *BRCA1* (5%)
- ○ C. *MEN1* (1%)
- ✓ ○ D. *MSH2* (47%)
- ○ E. *VHL* (4%)

Incorrect
Correct answer
D

47%
Answered correctly

04 secs
Time Spent

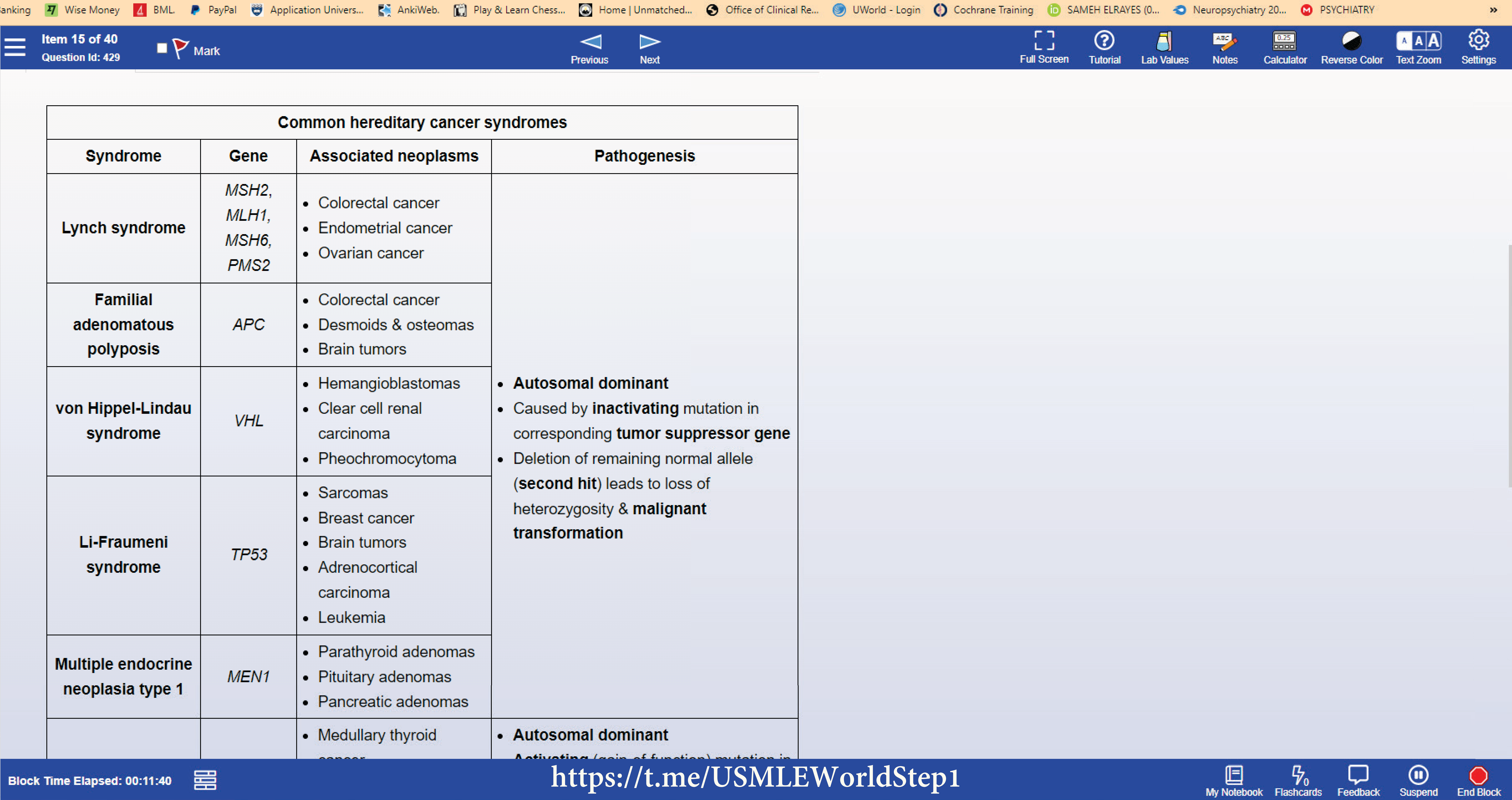
2023
Version

Explanation

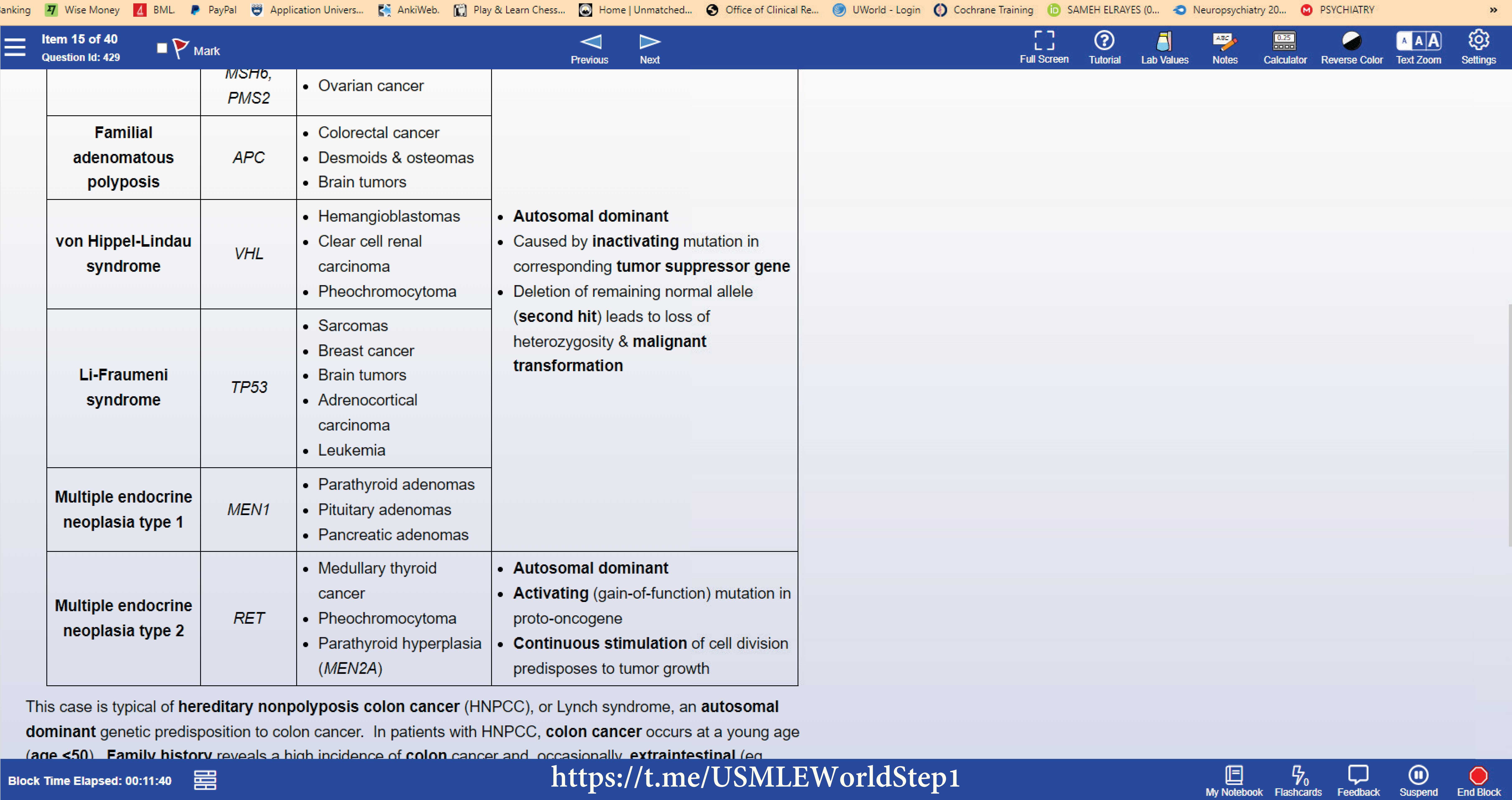
Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2*, *MLH1*, *MSH6*,	• Colorectal cancer • Endometrial cancer • Ovarian cancer	

Block Time Elapsed: 00:11:40

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 15 of 40
Question Id: 429
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:40
My Notebook
Flashcards
Feedback
Suspend
End Block

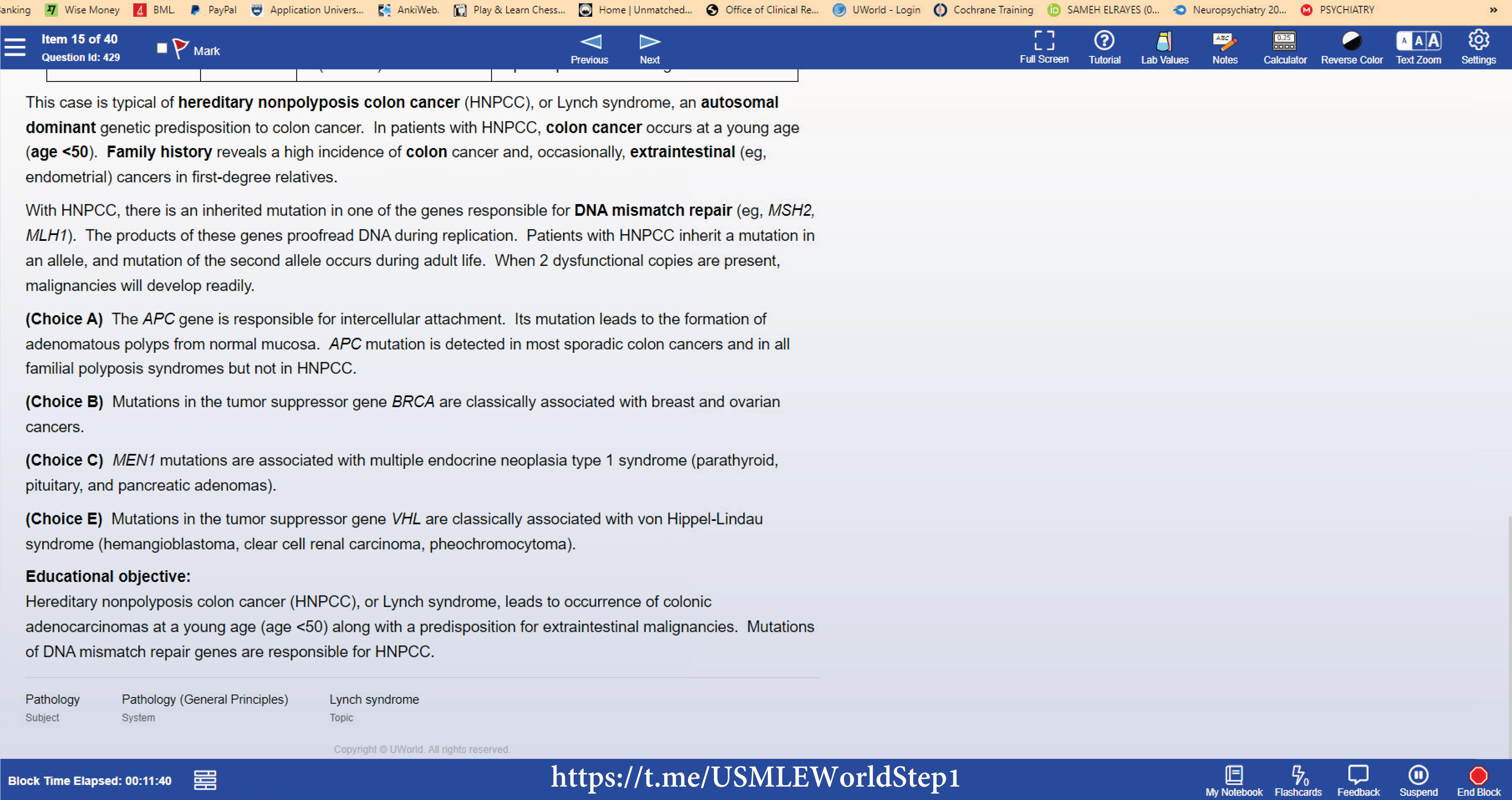
Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2*, *MLH1*, *MSH6*, *PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
		• Medullary thyroid	• **Autosomal dominant**


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 15 of 40
Question Id: 429
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

	MSH6, PMS2	- Ovarian cancer	- **Autosomal dominant** - Caused by **inactivating** mutation in corresponding **tumor suppressor gene** - Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Familial adenomatous polyposis	*APC*	- Colorectal cancer - Desmoids & osteomas - Brain tumors	
von Hippel-Lindau syndrome	*VHL*	- Hemangioblastomas - Clear cell renal carcinoma - Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	- Sarcomas - Breast cancer - Brain tumors - Adrenocortical carcinoma - Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	- Parathyroid adenomas - Pituitary adenomas - Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	- Medullary thyroid cancer - Pheochromocytoma - Parathyroid hyperplasia (*MEN2A*)	- **Autosomal dominant** - **Activating** (gain-of-function) mutation in proto-oncogene - **Continuous stimulation** of cell division predisposes to tumor growth

This case is typical of **hereditary nonpolyposis colon cancer** (HNPCC), or Lynch syndrome, an **autosomal dominant** genetic predisposition to colon cancer. In patients with HNPCC, **colon cancer** occurs at a young age (age <50). **Family history** reveals a high incidence of **colon** cancer and, occasionally, **extraintestinal** (eg

Block Time Elapsed: 00:11:40
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 15 of 40
Question Id: 429
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

This case is typical of **hereditary nonpolyposis colon cancer** (HNPCC), or Lynch syndrome, an **autosomal dominant** genetic predisposition to colon cancer. In patients with HNPCC, **colon cancer** occurs at a young age (**age <50**). **Family history** reveals a high incidence of **colon** cancer and, occasionally, **extraintestinal** (eg, endometrial) cancers in first-degree relatives.

With HNPCC, there is an inherited mutation in one of the genes responsible for **DNA mismatch repair** (eg, *MSH2, MLH1*). The products of these genes proofread DNA during replication. Patients with HNPCC inherit a mutation in an allele, and mutation of the second allele occurs during adult life. When 2 dysfunctional copies are present, malignancies will develop readily.

(Choice A) The *APC* gene is responsible for intercellular attachment. Its mutation leads to the formation of adenomatous polyps from normal mucosa. *APC* mutation is detected in most sporadic colon cancers and in all familial polyposis syndromes but not in HNPCC.

(Choice B) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice C) *MEN1* mutations are associated with multiple endocrine neoplasia type 1 syndrome (parathyroid, pituitary, and pancreatic adenomas).

(Choice E) Mutations in the tumor suppressor gene *VHL* are classically associated with von Hippel-Lindau syndrome (hemangioblastoma, clear cell renal carcinoma, pheochromocytoma).

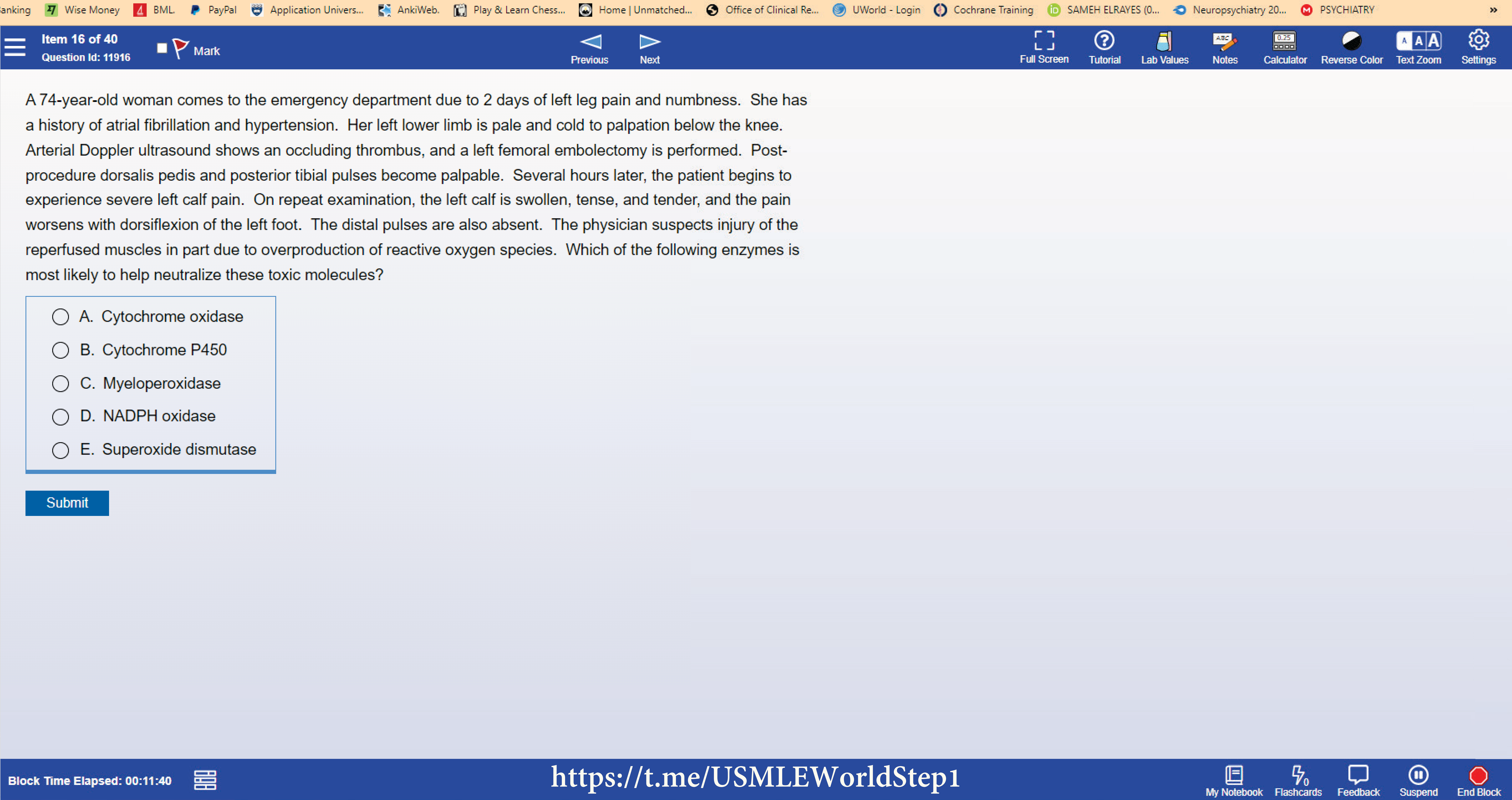
Educational objective:
Hereditary nonpolyposis colon cancer (HNPCC), or Lynch syndrome, leads to occurrence of colonic adenocarcinomas at a young age (age <50) along with a predisposition for extraintestinal malignancies. Mutations of DNA mismatch repair genes are responsible for HNPCC.

Pathology	Pathology (General Principles)	Lynch syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Block Time Elapsed: 00:11:40

My Notebook
Flashcards
Feedback
Suspend
End Block

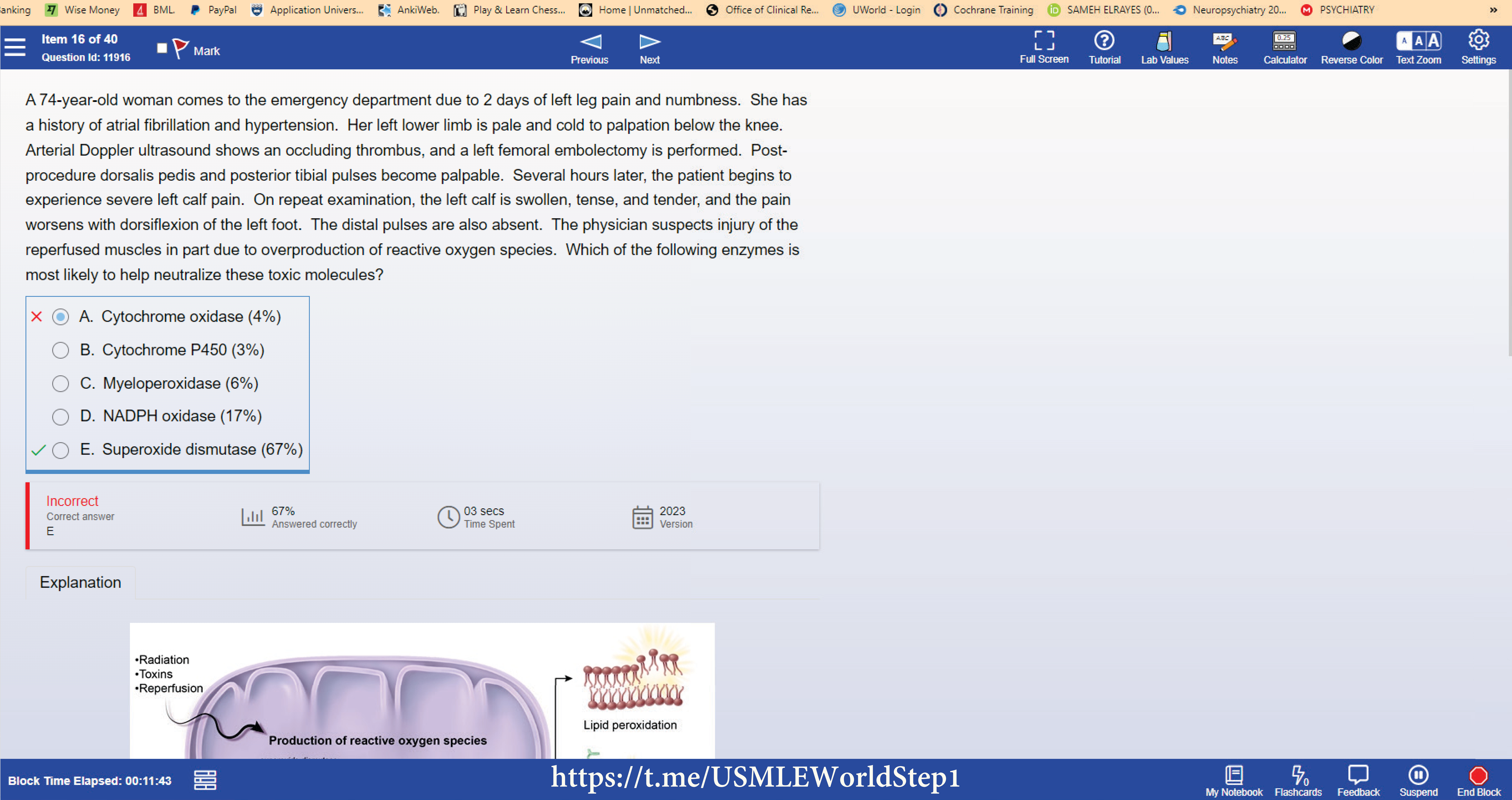

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 16 of 40
Question Id: 11916
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 74-year-old woman comes to the emergency department due to 2 days of left leg pain and numbness. She has a history of atrial fibrillation and hypertension. Her left lower limb is pale and cold to palpation below the knee. Arterial Doppler ultrasound shows an occluding thrombus, and a left femoral embolectomy is performed. Post-procedure dorsalis pedis and posterior tibial pulses become palpable. Several hours later, the patient begins to experience severe left calf pain. On repeat examination, the left calf is swollen, tense, and tender, and the pain worsens with dorsiflexion of the left foot. The distal pulses are also absent. The physician suspects injury of the reperfused muscles in part due to overproduction of reactive oxygen species. Which of the following enzymes is most likely to help neutralize these toxic molecules?

○ A. Cytochrome oxidase
○ B. Cytochrome P450
○ C. Myeloperoxidase
○ D. NADPH oxidase
○ E. Superoxide dismutase

Submit
Block Time Elapsed: 00:11:40

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 16 of 40
Question Id: 11916
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 74-year-old woman comes to the emergency department due to 2 days of left leg pain and numbness. She has a history of atrial fibrillation and hypertension. Her left lower limb is pale and cold to palpation below the knee. Arterial Doppler ultrasound shows an occluding thrombus, and a left femoral embolectomy is performed. Post-procedure dorsalis pedis and posterior tibial pulses become palpable. Several hours later, the patient begins to experience severe left calf pain. On repeat examination, the left calf is swollen, tense, and tender, and the pain worsens with dorsiflexion of the left foot. The distal pulses are also absent. The physician suspects injury of the reperfused muscles in part due to overproduction of reactive oxygen species. Which of the following enzymes is most likely to help neutralize these toxic molecules?

✗ ● A. Cytochrome oxidase (4%)

○ B. Cytochrome P450 (3%)

○ C. Myeloperoxidase (6%)

○ D. NADPH oxidase (17%)

✓ ○ E. Superoxide dismutase (67%)

Incorrect
Correct answer
E

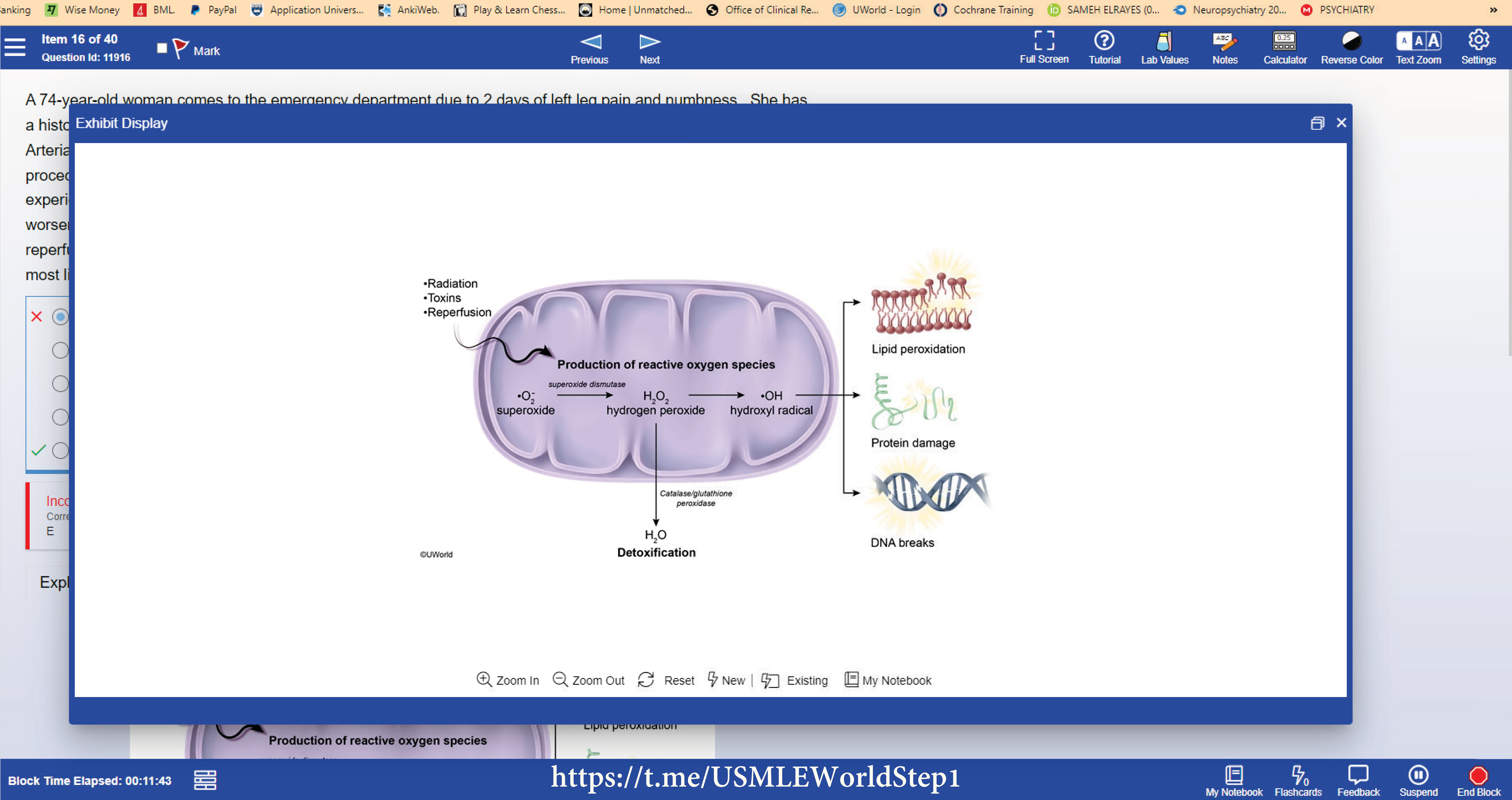
67%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

•Radiation
•Toxins
•Reperfusion
Production of reactive oxygen species
Lipid peroxidation
Block Time Elapsed: 00:11:43
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 16 of 40
Question Id: 11916
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
•Radiation
•Toxins
•Reperfusion
Production of reactive oxygen species
superoxide dismutase
•O_2^-
superoxide
H_2O_2
hydrogen peroxide
•OH
hydroxyl radical
Catalase/glutathione peroxidase
H_2O
Detoxification
Lipid peroxidation
Protein damage
DNA breaks
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:11:43
My Notebook
Flashcards
Feedback
Suspend
End Block

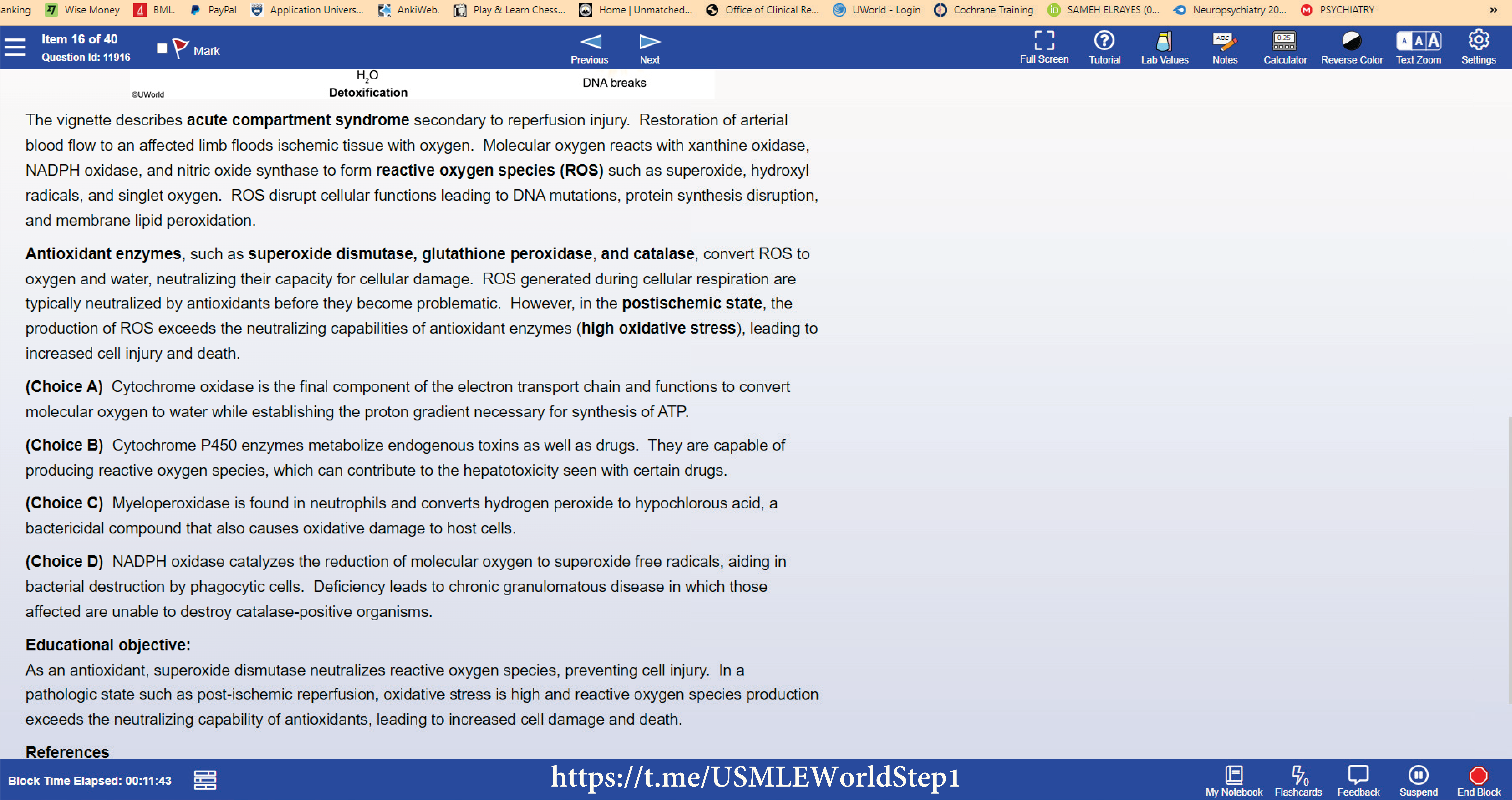
A 74-year-old woman comes to the emergency department due to 2 days of left leg pain and numbness. She has
a histo
Arteria
proced
experi
worse
reperf
most li

✕ ○
○
○
○
✓ ○

Inco
Corre
E

Expl

Production of reactive oxygen species
Lipid peroxidation


Item 16 of 40
Question Id: 11916
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
H_2O
Detoxification
DNA breaks
©UWorld
Block Time Elapsed: 00:11:43
My Notebook
Flashcards
Feedback
Suspend
End Block

The vignette describes **acute compartment syndrome** secondary to reperfusion injury. Restoration of arterial blood flow to an affected limb floods ischemic tissue with oxygen. Molecular oxygen reacts with xanthine oxidase, NADPH oxidase, and nitric oxide synthase to form **reactive oxygen species (ROS)** such as superoxide, hydroxyl radicals, and singlet oxygen. ROS disrupt cellular functions leading to DNA mutations, protein synthesis disruption, and membrane lipid peroxidation.

Antioxidant enzymes, such as **superoxide dismutase, glutathione peroxidase**, **and catalase**, convert ROS to oxygen and water, neutralizing their capacity for cellular damage. ROS generated during cellular respiration are typically neutralized by antioxidants before they become problematic. However, in the **postischemic state**, the production of ROS exceeds the neutralizing capabilities of antioxidant enzymes (**high oxidative stress**), leading to increased cell injury and death.

(Choice A) Cytochrome oxidase is the final component of the electron transport chain and functions to convert molecular oxygen to water while establishing the proton gradient necessary for synthesis of ATP.

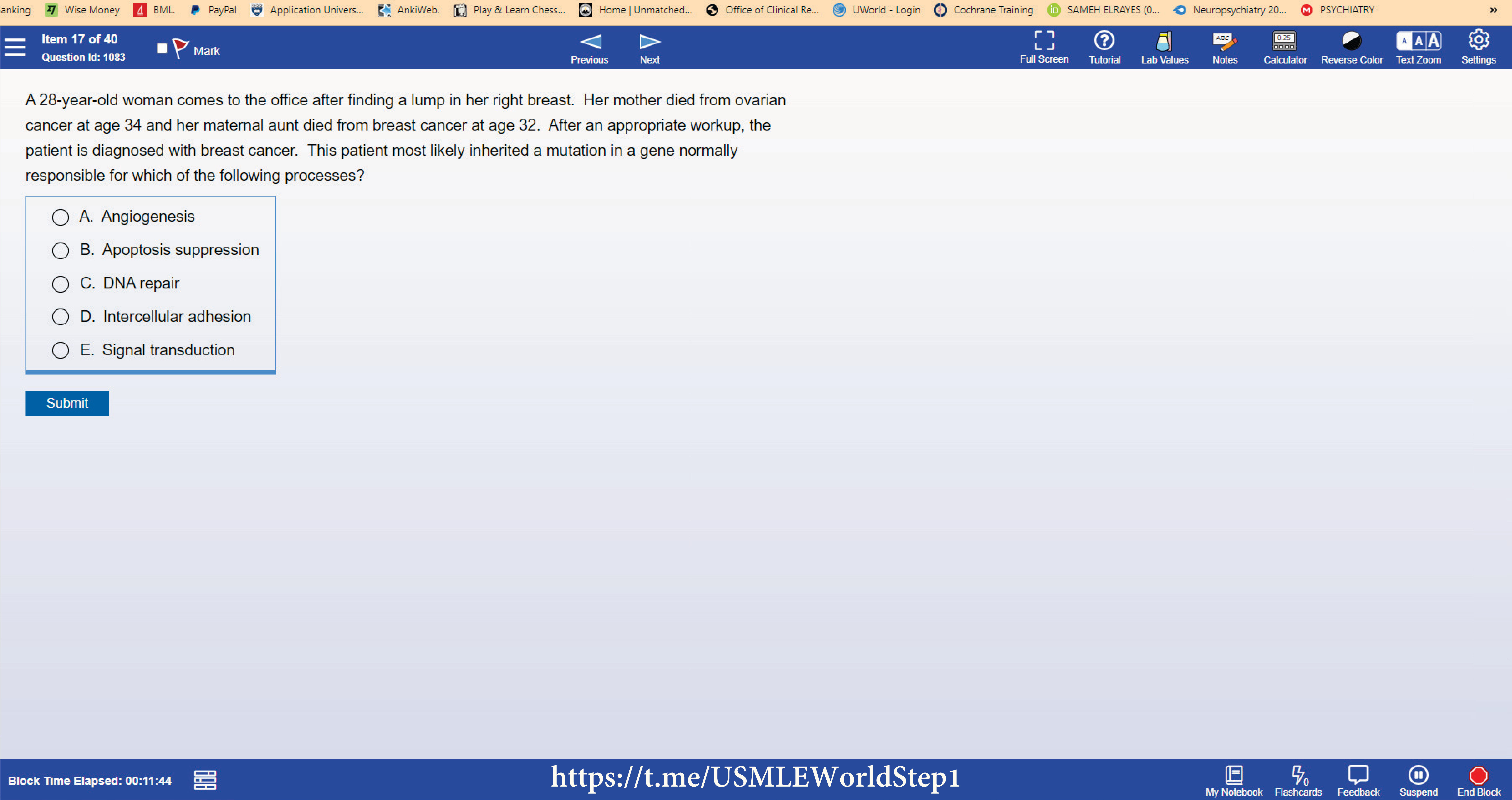
(Choice B) Cytochrome P450 enzymes metabolize endogenous toxins as well as drugs. They are capable of producing reactive oxygen species, which can contribute to the hepatotoxicity seen with certain drugs.

(Choice C) Myeloperoxidase is found in neutrophils and converts hydrogen peroxide to hypochlorous acid, a bactericidal compound that also causes oxidative damage to host cells.

(Choice D) NADPH oxidase catalyzes the reduction of molecular oxygen to superoxide free radicals, aiding in bacterial destruction by phagocytic cells. Deficiency leads to chronic granulomatous disease in which those affected are unable to destroy catalase-positive organisms.

Educational objective:
As an antioxidant, superoxide dismutase neutralizes reactive oxygen species, preventing cell injury. In a pathologic state such as post-ischemic reperfusion, oxidative stress is high and reactive oxygen species production exceeds the neutralizing capability of antioxidants, leading to increased cell damage and death.

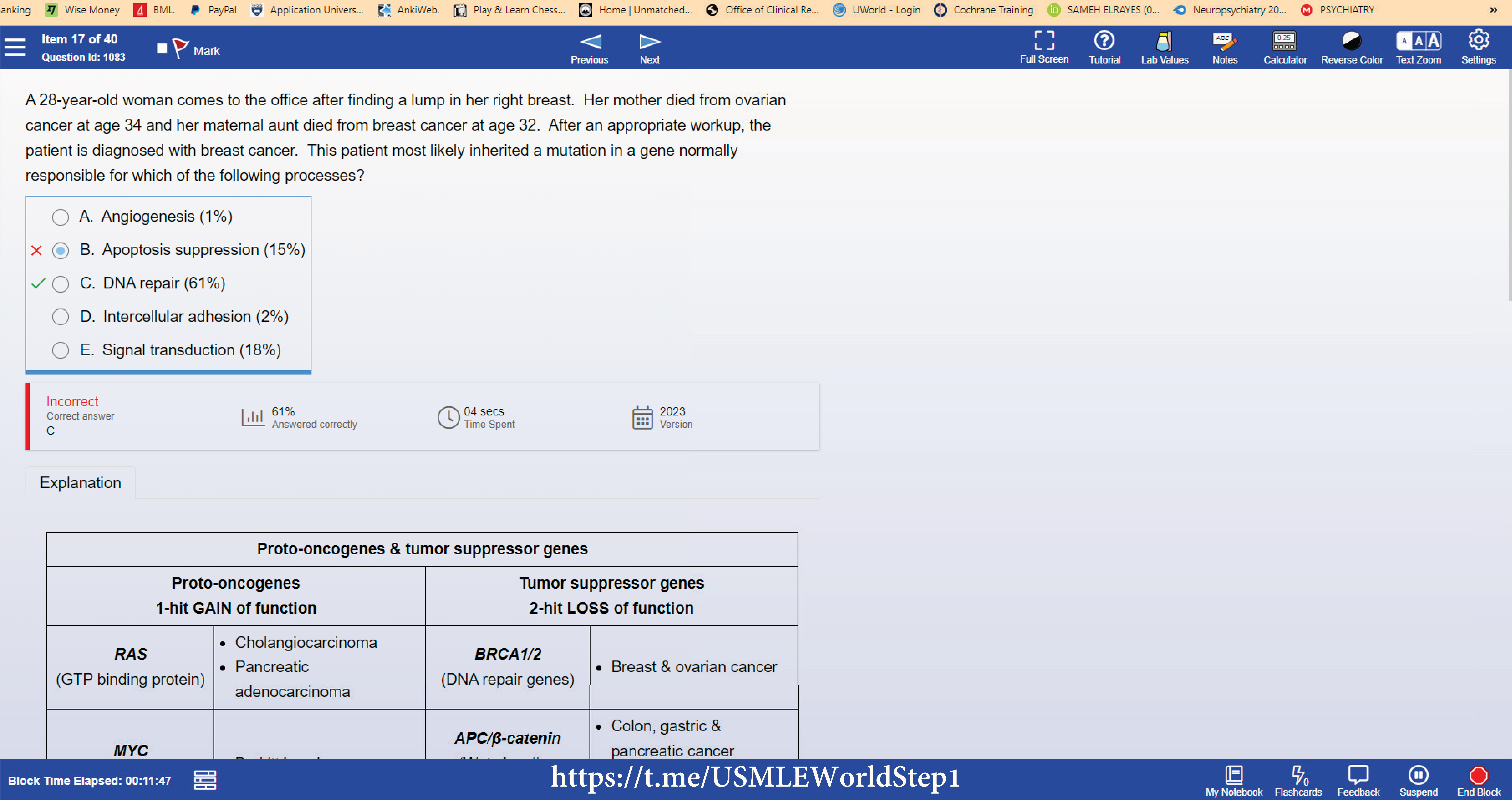
References


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 17 of 40
Question Id: 1083
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:44
My Notebook
Flashcards
Feedback
Suspend
End Block

A 28-year-old woman comes to the office after finding a lump in her right breast. Her mother died from ovarian cancer at age 34 and her maternal aunt died from breast cancer at age 32. After an appropriate workup, the patient is diagnosed with breast cancer. This patient most likely inherited a mutation in a gene normally responsible for which of the following processes?

○ A. Angiogenesis
○ B. Apoptosis suppression
○ C. DNA repair
○ D. Intercellular adhesion
○ E. Signal transduction

Submit


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 17 of 40
Question Id: 1083
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 28-year-old woman comes to the office after finding a lump in her right breast. Her mother died from ovarian cancer at age 34 and her maternal aunt died from breast cancer at age 32. After an appropriate workup, the patient is diagnosed with breast cancer. This patient most likely inherited a mutation in a gene normally responsible for which of the following processes?

○ A. Angiogenesis (1%)

✗ ● B. Apoptosis suppression (15%)

✓ ○ C. DNA repair (61%)

○ D. Intercellular adhesion (2%)

○ E. Signal transduction (18%)

Incorrect
Correct answer
C

61%
Answered correctly

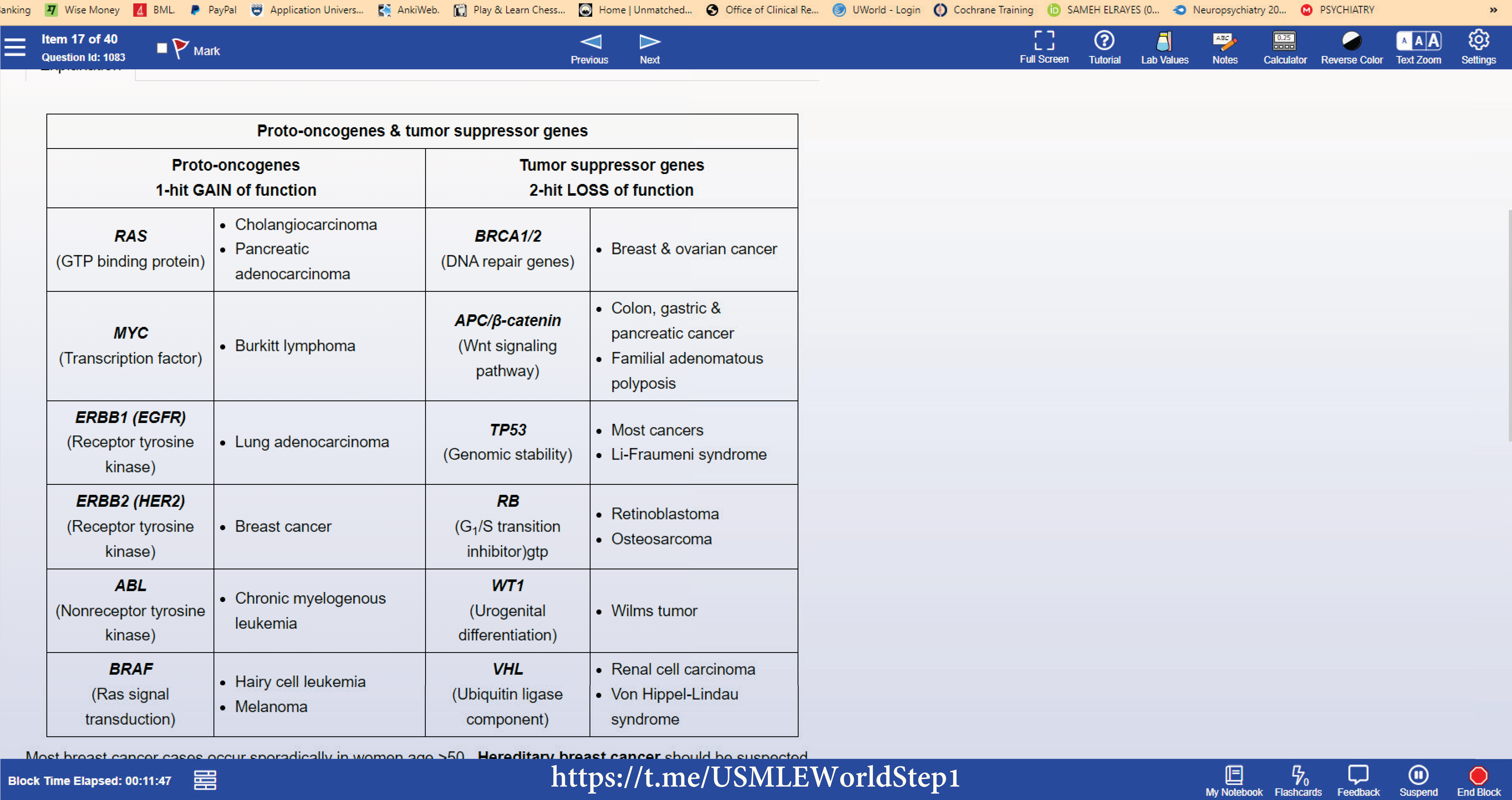
04 secs
Time Spent

2023
Version

Explanation

Proto-oncogenes & tumor suppressor genes			
Proto-oncogenes **1-hit GAIN of function**		**Tumor suppressor genes** **2-hit LOSS of function**	
RAS (GTP binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	• Breast & ovarian cancer
MYC		***APC/β-catenin***	• Colon, gastric & pancreatic cancer

Block Time Elapsed: 00:11:47
My Notebook
Flashcards
Feedback
Suspend
End Block

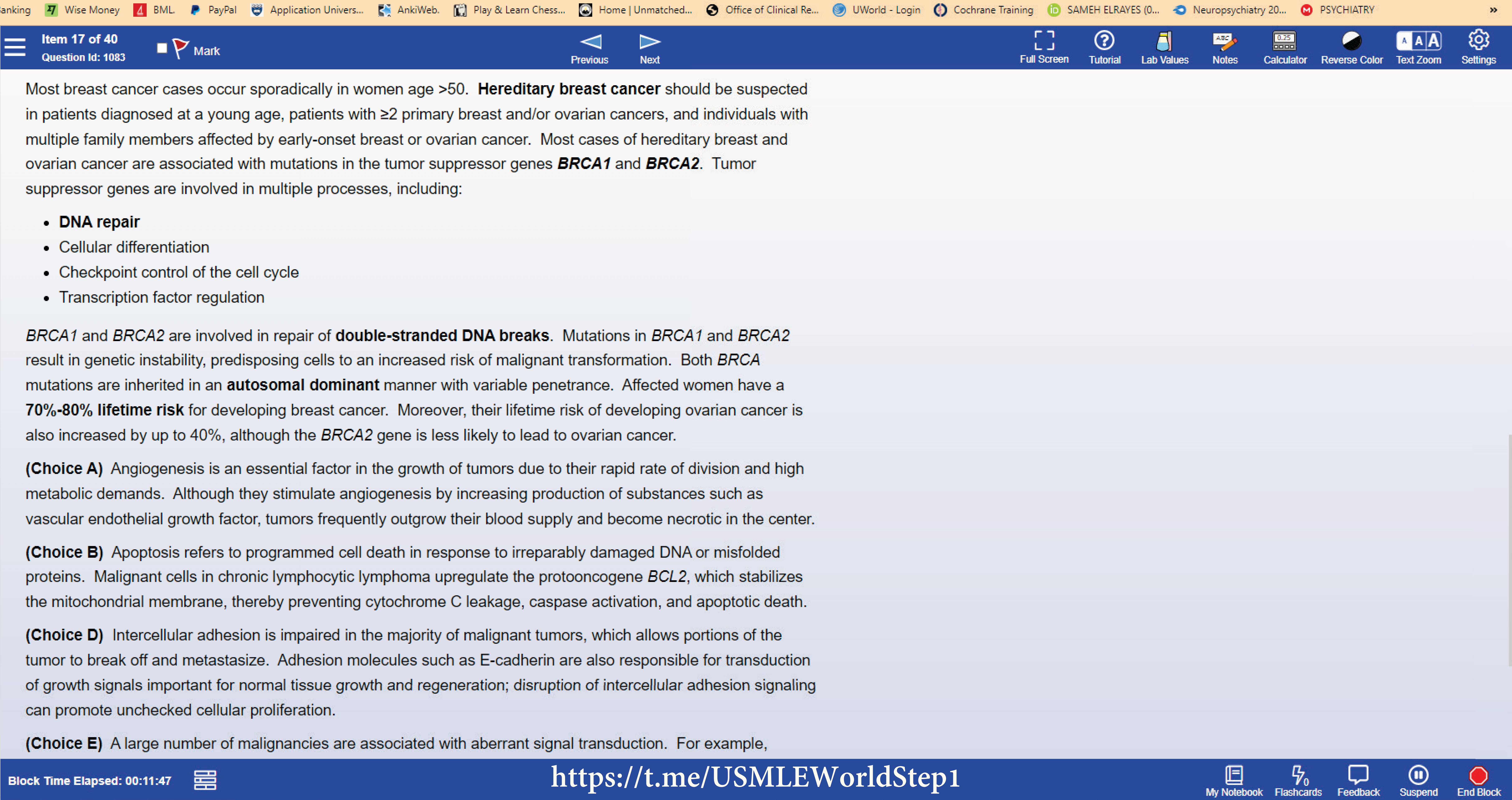

anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 17 of 40
Question Id: 1083
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Proto-oncogenes & tumor suppressor genes			
Proto-oncogenes **1-hit GAIN of function**		**Tumor suppressor genes** **2-hit LOSS of function**	
RAS (GTP binding protein)	- Cholangiocarcinoma - Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	- Breast & ovarian cancer
MYC (Transcription factor)	- Burkitt lymphoma	***APC/β-catenin*** (Wnt signaling pathway)	- Colon, gastric & pancreatic cancer - Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	- Lung adenocarcinoma	***TP53*** (Genomic stability)	- Most cancers - Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	- Breast cancer	***RB*** (G_1/S transition inhibitor)gtp	- Retinoblastoma - Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	- Chronic myelogenous leukemia	***WT1*** (Urogenital differentiation)	- Wilms tumor
BRAF (Ras signal transduction)	- Hairy cell leukemia - Melanoma	***VHL*** (Ubiquitin ligase component)	- Renal cell carcinoma - Von Hippel-Lindau syndrome

Most breast cancer cases occur sporadically in women age >50. **Hereditary breast cancer** should be suspected

Block Time Elapsed: 00:11:47

My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 17 of 40
Question Id: 1083
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Most breast cancer cases occur sporadically in women age >50. **Hereditary breast cancer** should be suspected in patients diagnosed at a young age, patients with ≥2 primary breast and/or ovarian cancers, and individuals with multiple family members affected by early-onset breast or ovarian cancer. Most cases of hereditary breast and ovarian cancer are associated with mutations in the tumor suppressor genes ***BRCA1*** and ***BRCA2***. Tumor suppressor genes are involved in multiple processes, including:

- **DNA repair**
- Cellular differentiation
- Checkpoint control of the cell cycle
- Transcription factor regulation

BRCA1 and *BRCA2* are involved in repair of **double-stranded DNA breaks**. Mutations in *BRCA1* and *BRCA2* result in genetic instability, predisposing cells to an increased risk of malignant transformation. Both *BRCA* mutations are inherited in an **autosomal dominant** manner with variable penetrance. Affected women have a **70%-80% lifetime risk** for developing breast cancer. Moreover, their lifetime risk of developing ovarian cancer is also increased by up to 40%, although the *BRCA2* gene is less likely to lead to ovarian cancer.

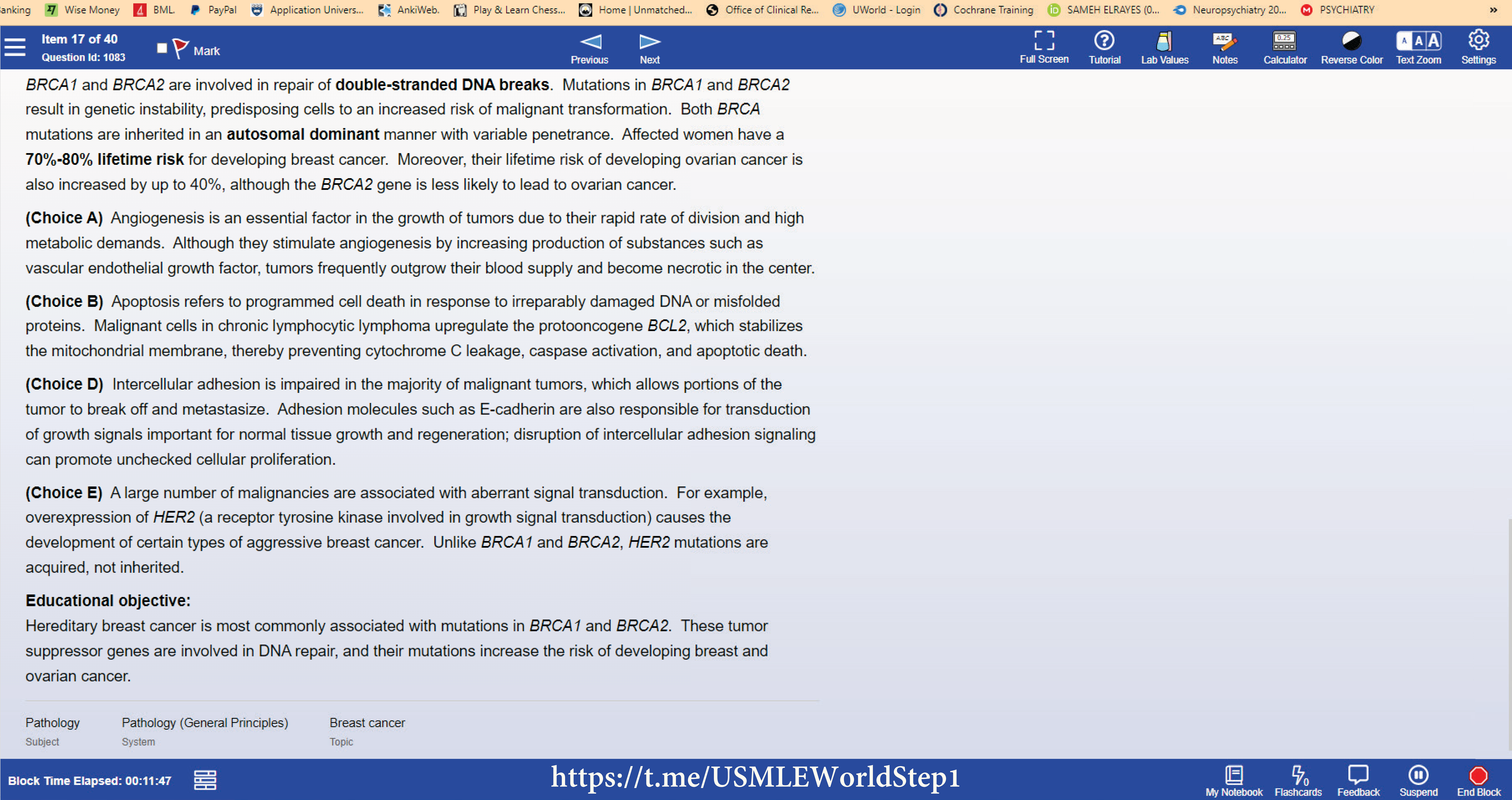
(Choice A) Angiogenesis is an essential factor in the growth of tumors due to their rapid rate of division and high metabolic demands. Although they stimulate angiogenesis by increasing production of substances such as vascular endothelial growth factor, tumors frequently outgrow their blood supply and become necrotic in the center.

(Choice B) Apoptosis refers to programmed cell death in response to irreparably damaged DNA or misfolded proteins. Malignant cells in chronic lymphocytic lymphoma upregulate the protooncogene *BCL2*, which stabilizes the mitochondrial membrane, thereby preventing cytochrome C leakage, caspase activation, and apoptotic death.

(Choice D) Intercellular adhesion is impaired in the majority of malignant tumors, which allows portions of the tumor to break off and metastasize. Adhesion molecules such as E-cadherin are also responsible for transduction of growth signals important for normal tissue growth and regeneration; disruption of intercellular adhesion signaling can promote unchecked cellular proliferation.

(Choice E) A large number of malignancies are associated with aberrant signal transduction. For example,

Block Time Elapsed: 00:11:47
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 17 of 40
Question Id: 1083
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

BRCA1 and *BRCA2* are involved in repair of **double-stranded DNA breaks**. Mutations in *BRCA1* and *BRCA2* result in genetic instability, predisposing cells to an increased risk of malignant transformation. Both *BRCA* mutations are inherited in an **autosomal dominant** manner with variable penetrance. Affected women have a **70%-80% lifetime risk** for developing breast cancer. Moreover, their lifetime risk of developing ovarian cancer is also increased by up to 40%, although the *BRCA2* gene is less likely to lead to ovarian cancer.

(Choice A) Angiogenesis is an essential factor in the growth of tumors due to their rapid rate of division and high metabolic demands. Although they stimulate angiogenesis by increasing production of substances such as vascular endothelial growth factor, tumors frequently outgrow their blood supply and become necrotic in the center.

(Choice B) Apoptosis refers to programmed cell death in response to irreparably damaged DNA or misfolded proteins. Malignant cells in chronic lymphocytic lymphoma upregulate the protooncogene *BCL2*, which stabilizes the mitochondrial membrane, thereby preventing cytochrome C leakage, caspase activation, and apoptotic death.

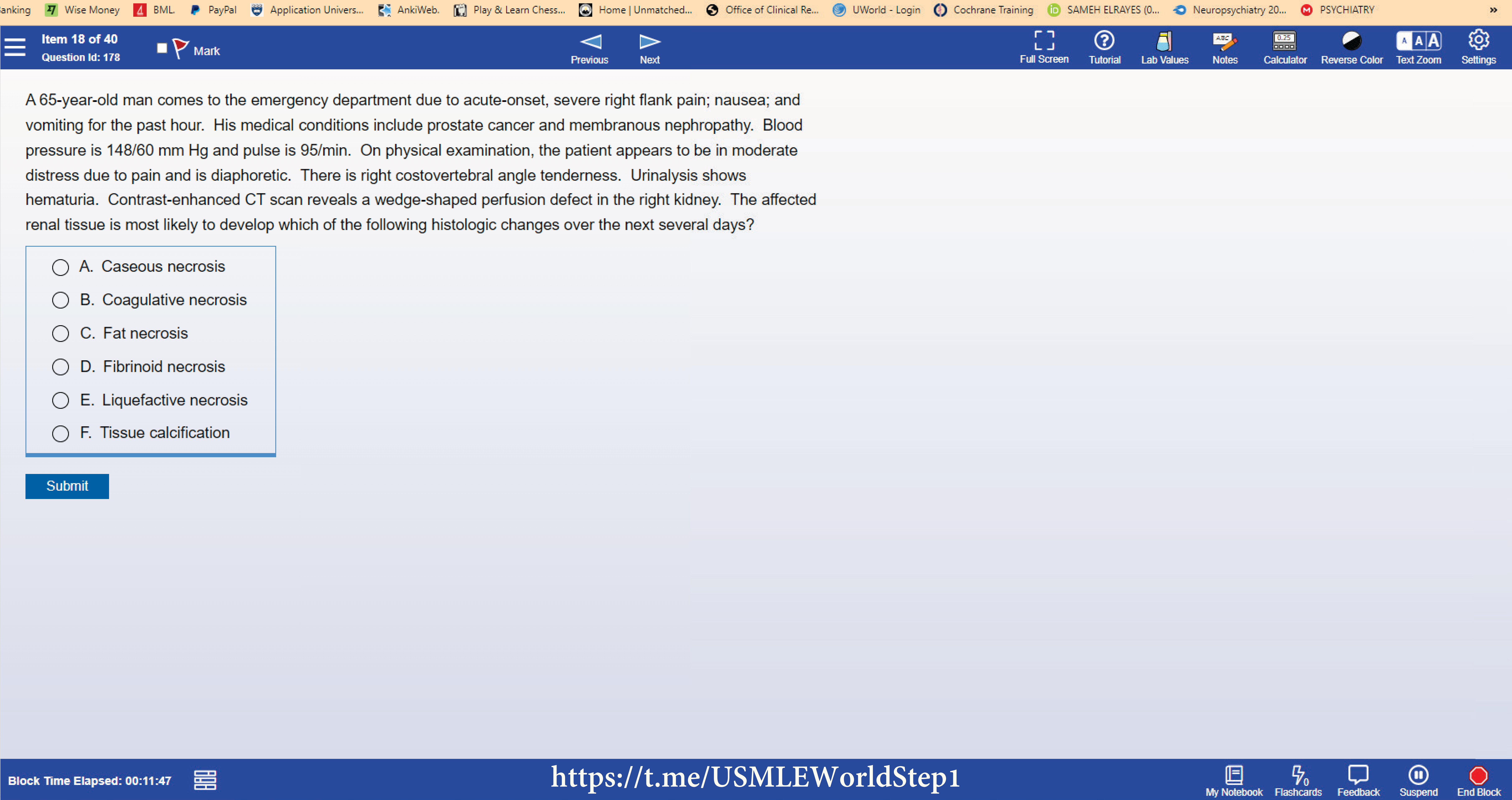
(Choice D) Intercellular adhesion is impaired in the majority of malignant tumors, which allows portions of the tumor to break off and metastasize. Adhesion molecules such as E-cadherin are also responsible for transduction of growth signals important for normal tissue growth and regeneration; disruption of intercellular adhesion signaling can promote unchecked cellular proliferation.

(Choice E) A large number of malignancies are associated with aberrant signal transduction. For example, overexpression of *HER2* (a receptor tyrosine kinase involved in growth signal transduction) causes the development of certain types of aggressive breast cancer. Unlike *BRCA1* and *BRCA2*, *HER2* mutations are acquired, not inherited.

Educational objective:
Hereditary breast cancer is most commonly associated with mutations in *BRCA1* and *BRCA2*. These tumor suppressor genes are involved in DNA repair, and their mutations increase the risk of developing breast and ovarian cancer.

Pathology	Pathology (General Principles)	Breast cancer
Subject	System	Topic

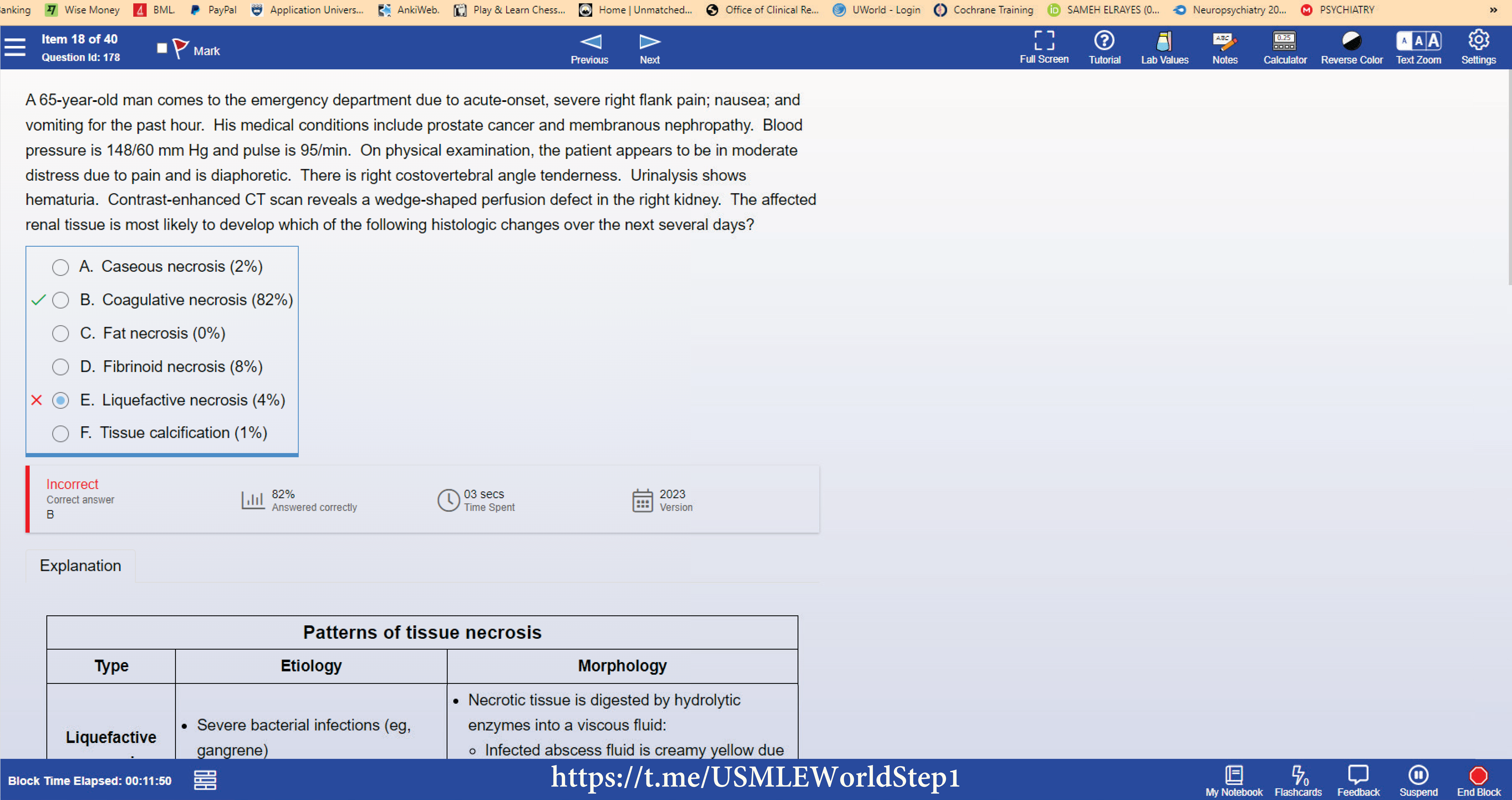
Block Time Elapsed: 00:11:47
https://t.me/USMLEWorldStep1
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 18 of 40
Question Id: 178
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 65-year-old man comes to the emergency department due to acute-onset, severe right flank pain; nausea; and vomiting for the past hour. His medical conditions include prostate cancer and membranous nephropathy. Blood pressure is 148/60 mm Hg and pulse is 95/min. On physical examination, the patient appears to be in moderate distress due to pain and is diaphoretic. There is right costovertebral angle tenderness. Urinalysis shows hematuria. Contrast-enhanced CT scan reveals a wedge-shaped perfusion defect in the right kidney. The affected renal tissue is most likely to develop which of the following histologic changes over the next several days?

○ A. Caseous necrosis
○ B. Coagulative necrosis
○ C. Fat necrosis
○ D. Fibrinoid necrosis
○ E. Liquefactive necrosis
○ F. Tissue calcification

Submit
Block Time Elapsed: 00:11:47
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 18 of 40
Question Id: 178
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 65-year-old man comes to the emergency department due to acute-onset, severe right flank pain; nausea; and vomiting for the past hour. His medical conditions include prostate cancer and membranous nephropathy. Blood pressure is 148/60 mm Hg and pulse is 95/min. On physical examination, the patient appears to be in moderate distress due to pain and is diaphoretic. There is right costovertebral angle tenderness. Urinalysis shows hematuria. Contrast-enhanced CT scan reveals a wedge-shaped perfusion defect in the right kidney. The affected renal tissue is most likely to develop which of the following histologic changes over the next several days?

○ A. Caseous necrosis (2%)
✓ ○ B. Coagulative necrosis (82%)
○ C. Fat necrosis (0%)
○ D. Fibrinoid necrosis (8%)
✗ ● E. Liquefactive necrosis (4%)
○ F. Tissue calcification (1%)

Incorrect
Correct answer
B

82%
Answered correctly

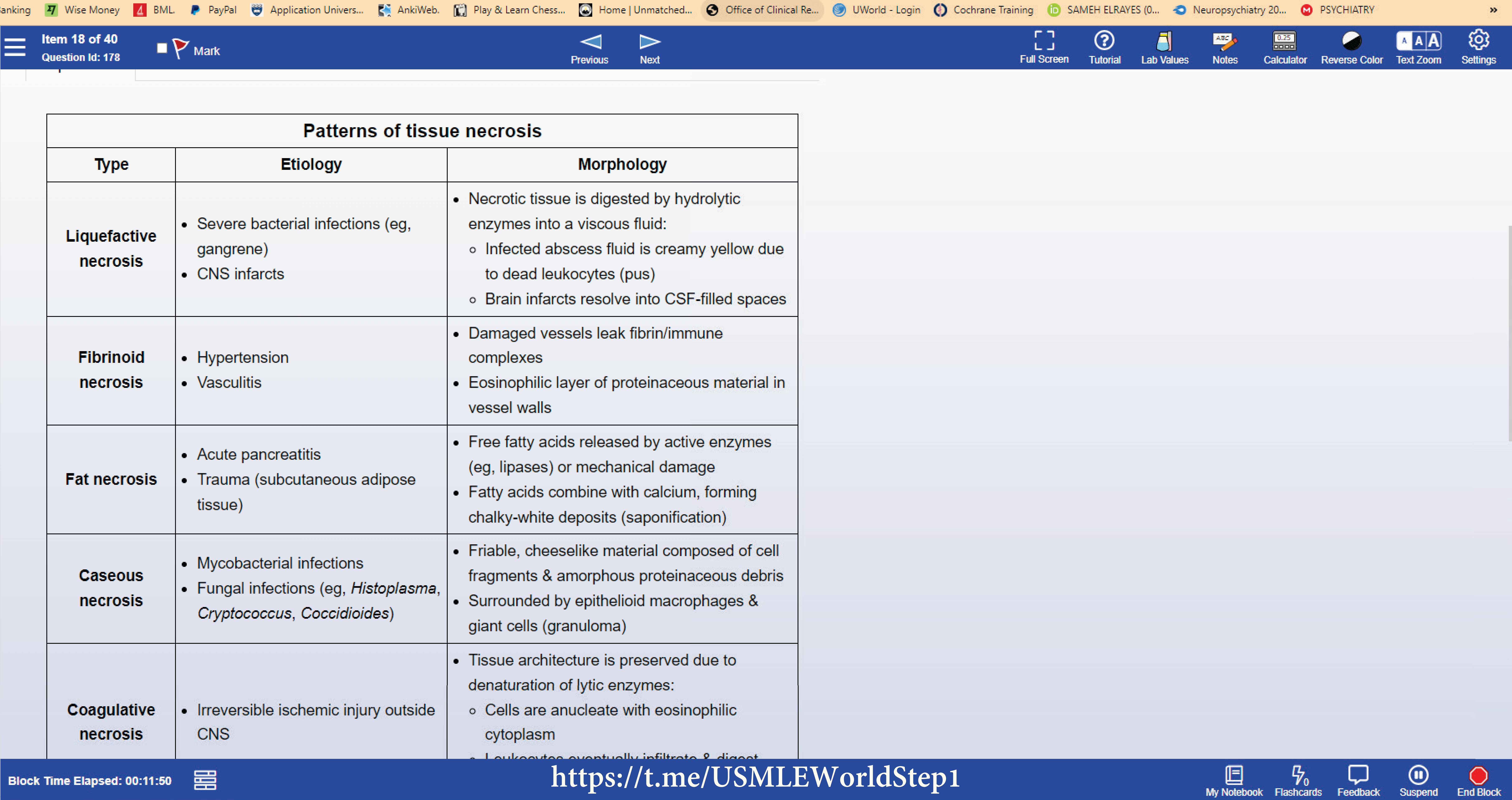
03 secs
Time Spent

2023
Version

Explanation

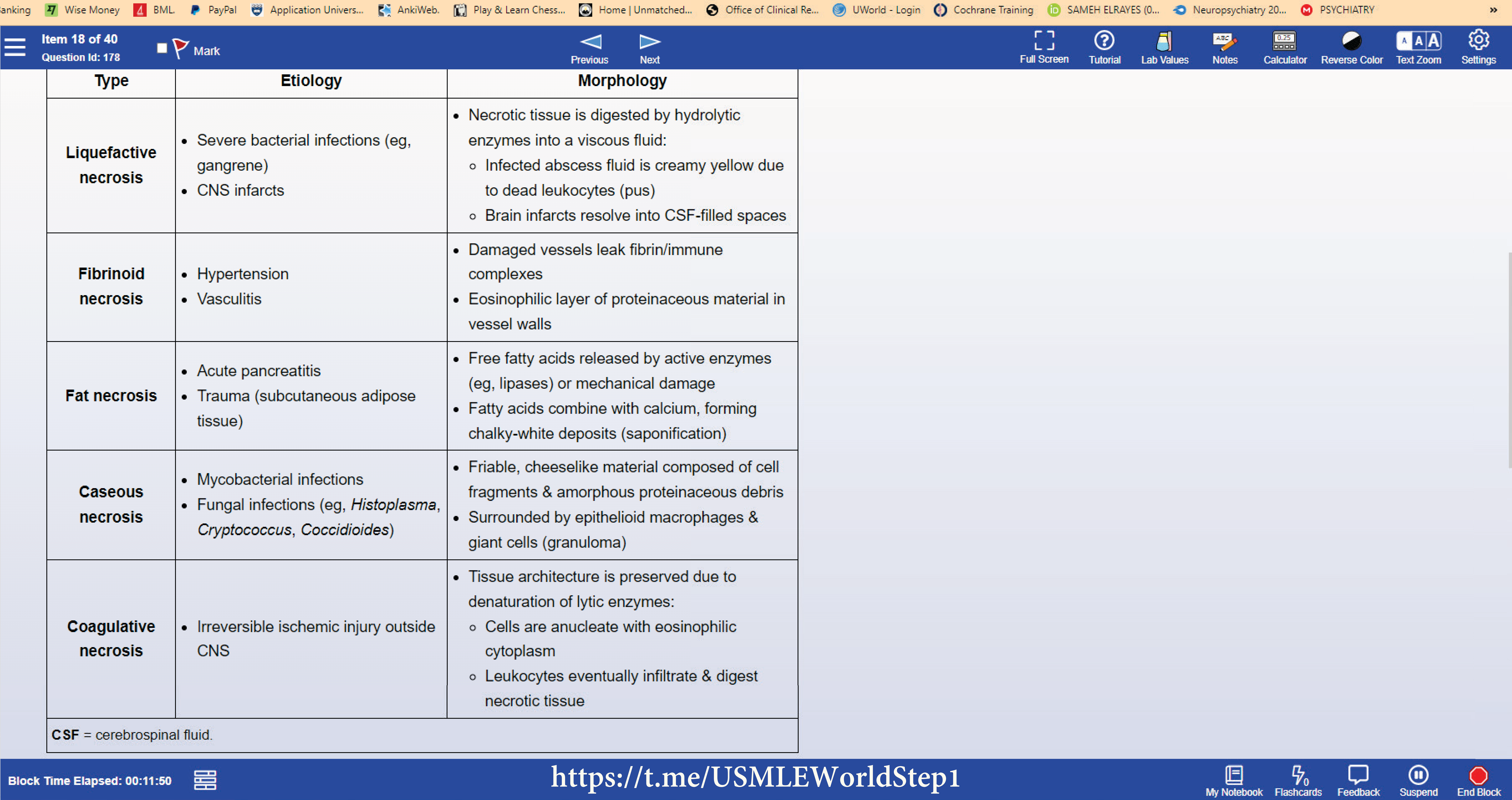
Patterns of tissue necrosis		
Type	**Etiology**	**Morphology**
Liquefactive	• Severe bacterial infections (eg, gangrene)	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ∘ Infected abscess fluid is creamy yellow due

Block Time Elapsed: 00:11:50
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 18 of 40
Question Id: 178
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:50
My Notebook
Flashcards
Feedback
Suspend
End Block

Patterns of tissue necrosis

Type	Etiology	Morphology
Liquefactive necrosis	• Severe bacterial infections (eg, gangrene) • CNS infarcts	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ○ Infected abscess fluid is creamy yellow due to dead leukocytes (pus) ○ Brain infarcts resolve into CSF-filled spaces
Fibrinoid necrosis	• Hypertension • Vasculitis	• Damaged vessels leak fibrin/immune complexes • Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	• Acute pancreatitis • Trauma (subcutaneous adipose tissue)	• Free fatty acids released by active enzymes (eg, lipases) or mechanical damage • Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	• Mycobacterial infections • Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	• Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris • Surrounded by epithelioid macrophages & giant cells (granuloma)
Coagulative necrosis	• Irreversible ischemic injury outside CNS	• Tissue architecture is preserved due to denaturation of lytic enzymes: ○ Cells are anucleate with eosinophilic cytoplasm ○ Leukocytes eventually infiltrate & digest



anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 18 of 40
Question Id: 178
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:50
My Notebook
Flashcards
Feedback
Suspend
End Block

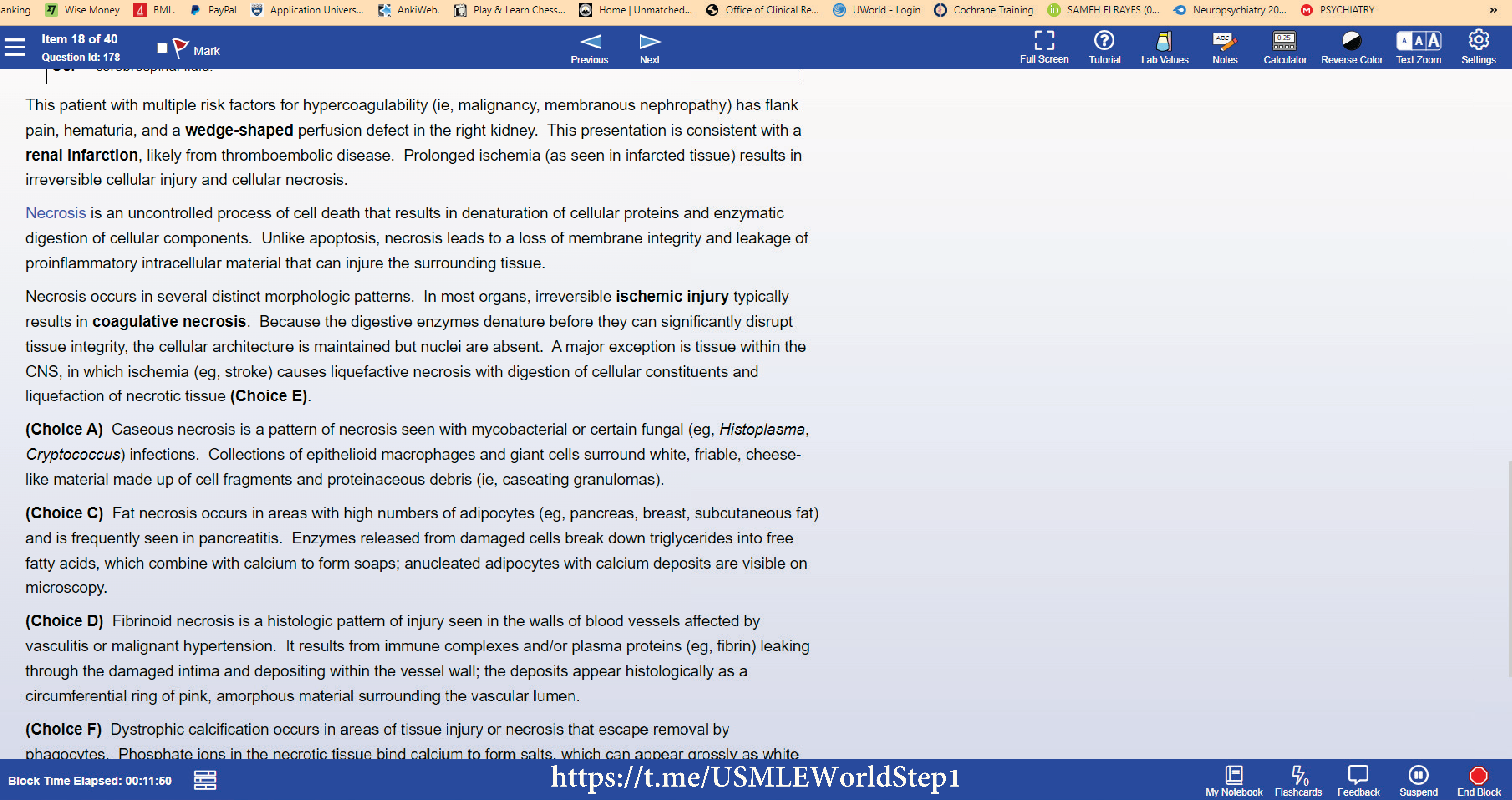
Type	Etiology	Morphology

Liquefactive necrosis	- Severe bacterial infections (eg, gangrene)
	- CNS infarcts
		- Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid:
		  ○ Infected abscess fluid is creamy yellow due to dead leukocytes (pus)
		  ○ Brain infarcts resolve into CSF-filled spaces

Fibrinoid necrosis	- Hypertension - Vasculitis	- Damaged vessels leak fibrin/immune complexes - Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	- Acute pancreatitis - Trauma (subcutaneous adipose tissue)	- Free fatty acids released by active enzymes (eg, lipases) or mechanical damage - Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	- Mycobacterial infections - Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	- Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris - Surrounded by epithelioid macrophages & giant cells (granuloma)

Coagulative necrosis	- Irreversible ischemic injury outside CNS	- Tissue architecture is preserved due to denaturation of lytic enzymes:
		  ○ Cells are anucleate with eosinophilic cytoplasm
		  ○ Leukocytes eventually infiltrate & digest necrotic tissue

CSF = cerebrospinal fluid.



This patient with multiple risk factors for hypercoagulability (ie, malignancy, membranous nephropathy) has flank pain, hematuria, and a **wedge-shaped** perfusion defect in the right kidney. This presentation is consistent with a **renal infarction**, likely from thromboembolic disease. Prolonged ischemia (as seen in infarcted tissue) results in irreversible cellular injury and cellular necrosis.

Necrosis is an uncontrolled process of cell death that results in denaturation of cellular proteins and enzymatic digestion of cellular components. Unlike apoptosis, necrosis leads to a loss of membrane integrity and leakage of proinflammatory intracellular material that can injure the surrounding tissue.

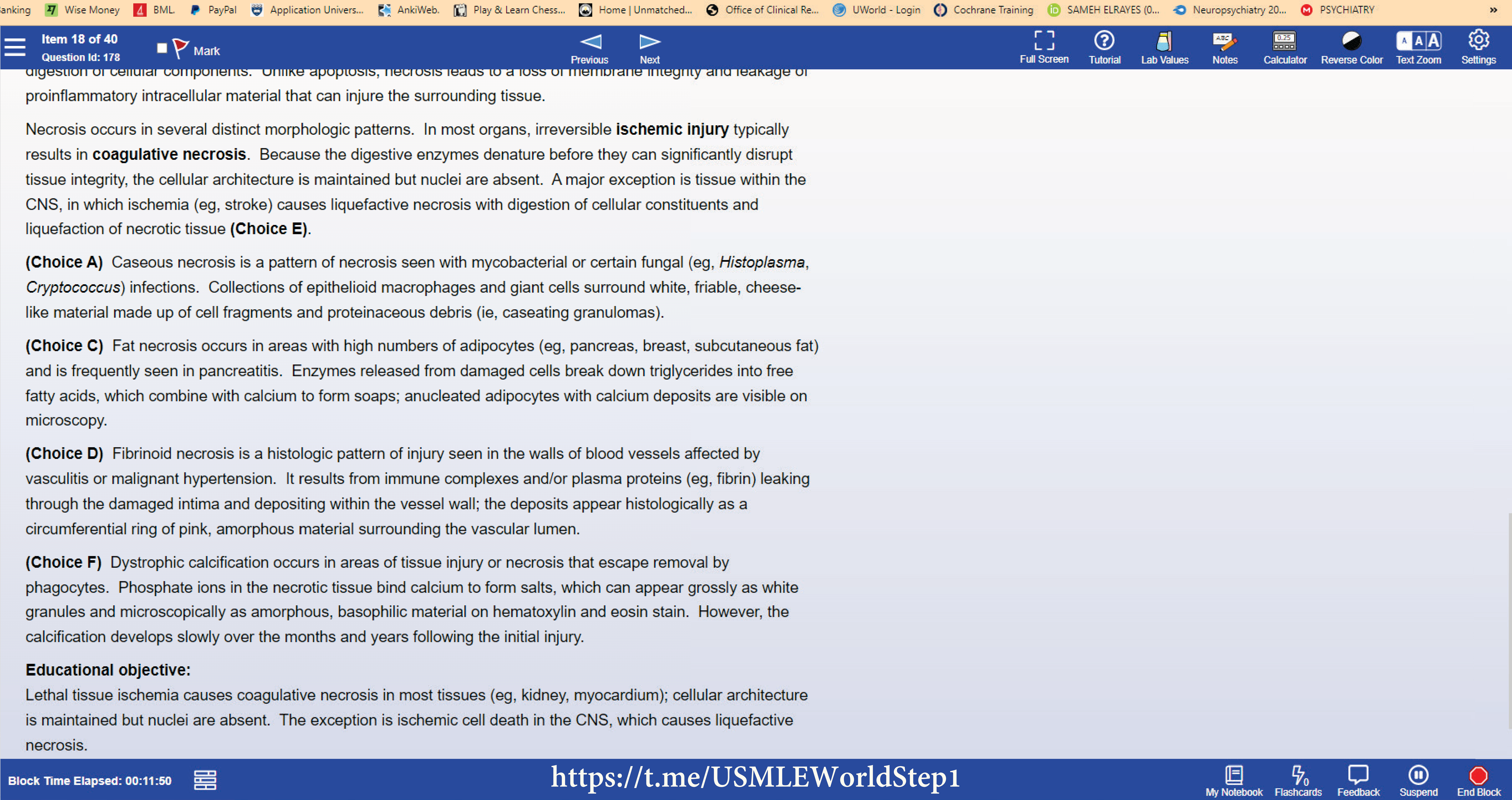
Necrosis occurs in several distinct morphologic patterns. In most organs, irreversible **ischemic injury** typically results in **coagulative necrosis**. Because the digestive enzymes denature before they can significantly disrupt tissue integrity, the cellular architecture is maintained but nuclei are absent. A major exception is tissue within the CNS, in which ischemia (eg, stroke) causes liquefactive necrosis with digestion of cellular constituents and liquefaction of necrotic tissue **(Choice E)**.

(Choice A) Caseous necrosis is a pattern of necrosis seen with mycobacterial or certain fungal (eg, *Histoplasma*, *Cryptococcus*) infections. Collections of epithelioid macrophages and giant cells surround white, friable, cheese-like material made up of cell fragments and proteinaceous debris (ie, caseating granulomas).

(Choice C) Fat necrosis occurs in areas with high numbers of adipocytes (eg, pancreas, breast, subcutaneous fat) and is frequently seen in pancreatitis. Enzymes released from damaged cells break down triglycerides into free fatty acids, which combine with calcium to form soaps; anucleated adipocytes with calcium deposits are visible on microscopy.

(Choice D) Fibrinoid necrosis is a histologic pattern of injury seen in the walls of blood vessels affected by vasculitis or malignant hypertension. It results from immune complexes and/or plasma proteins (eg, fibrin) leaking through the damaged intima and depositing within the vessel wall; the deposits appear histologically as a circumferential ring of pink, amorphous material surrounding the vascular lumen.

(Choice F) Dystrophic calcification occurs in areas of tissue injury or necrosis that escape removal by phagocytes. Phosphate ions in the necrotic tissue bind calcium to form salts, which can appear grossly as white


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 18 of 40
Question Id: 178
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

digestion of cellular components. Unlike apoptosis, necrosis leads to a loss of membrane integrity and leakage of proinflammatory intracellular material that can injure the surrounding tissue.

Necrosis occurs in several distinct morphologic patterns. In most organs, irreversible **ischemic injury** typically results in **coagulative necrosis**. Because the digestive enzymes denature before they can significantly disrupt tissue integrity, the cellular architecture is maintained but nuclei are absent. A major exception is tissue within the CNS, in which ischemia (eg, stroke) causes liquefactive necrosis with digestion of cellular constituents and liquefaction of necrotic tissue **(Choice E)**.

(Choice A) Caseous necrosis is a pattern of necrosis seen with mycobacterial or certain fungal (eg, *Histoplasma*, *Cryptococcus*) infections. Collections of epithelioid macrophages and giant cells surround white, friable, cheese-like material made up of cell fragments and proteinaceous debris (ie, caseating granulomas).

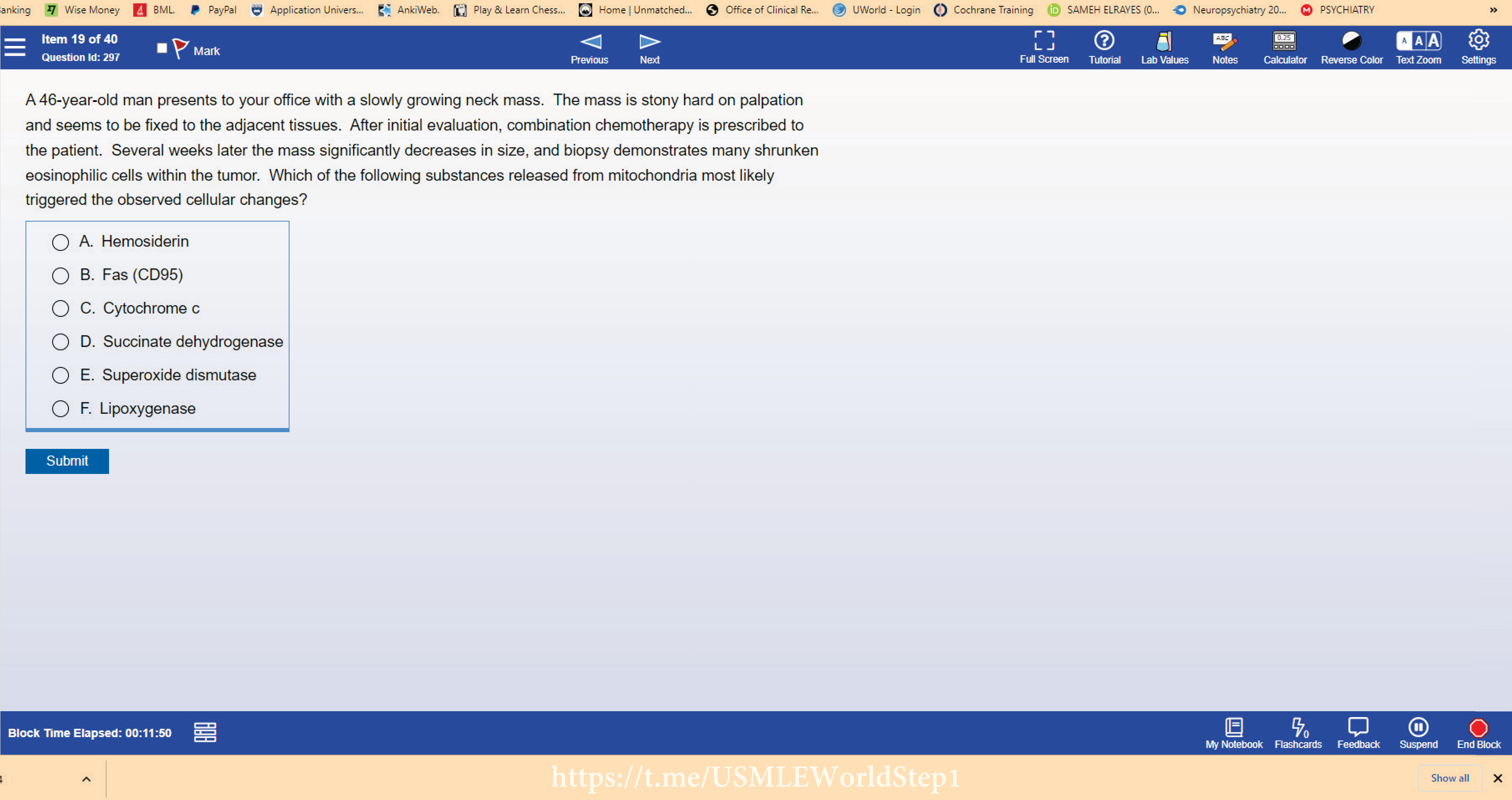
(Choice C) Fat necrosis occurs in areas with high numbers of adipocytes (eg, pancreas, breast, subcutaneous fat) and is frequently seen in pancreatitis. Enzymes released from damaged cells break down triglycerides into free fatty acids, which combine with calcium to form soaps; anucleated adipocytes with calcium deposits are visible on microscopy.

(Choice D) Fibrinoid necrosis is a histologic pattern of injury seen in the walls of blood vessels affected by vasculitis or malignant hypertension. It results from immune complexes and/or plasma proteins (eg, fibrin) leaking through the damaged intima and depositing within the vessel wall; the deposits appear histologically as a circumferential ring of pink, amorphous material surrounding the vascular lumen.

(Choice F) Dystrophic calcification occurs in areas of tissue injury or necrosis that escape removal by phagocytes. Phosphate ions in the necrotic tissue bind calcium to form salts, which can appear grossly as white granules and microscopically as amorphous, basophilic material on hematoxylin and eosin stain. However, the calcification develops slowly over the months and years following the initial injury.

Educational objective:
Lethal tissue ischemia causes coagulative necrosis in most tissues (eg, kidney, myocardium); cellular architecture is maintained but nuclei are absent. The exception is ischemic cell death in the CNS, which causes liquefactive necrosis.

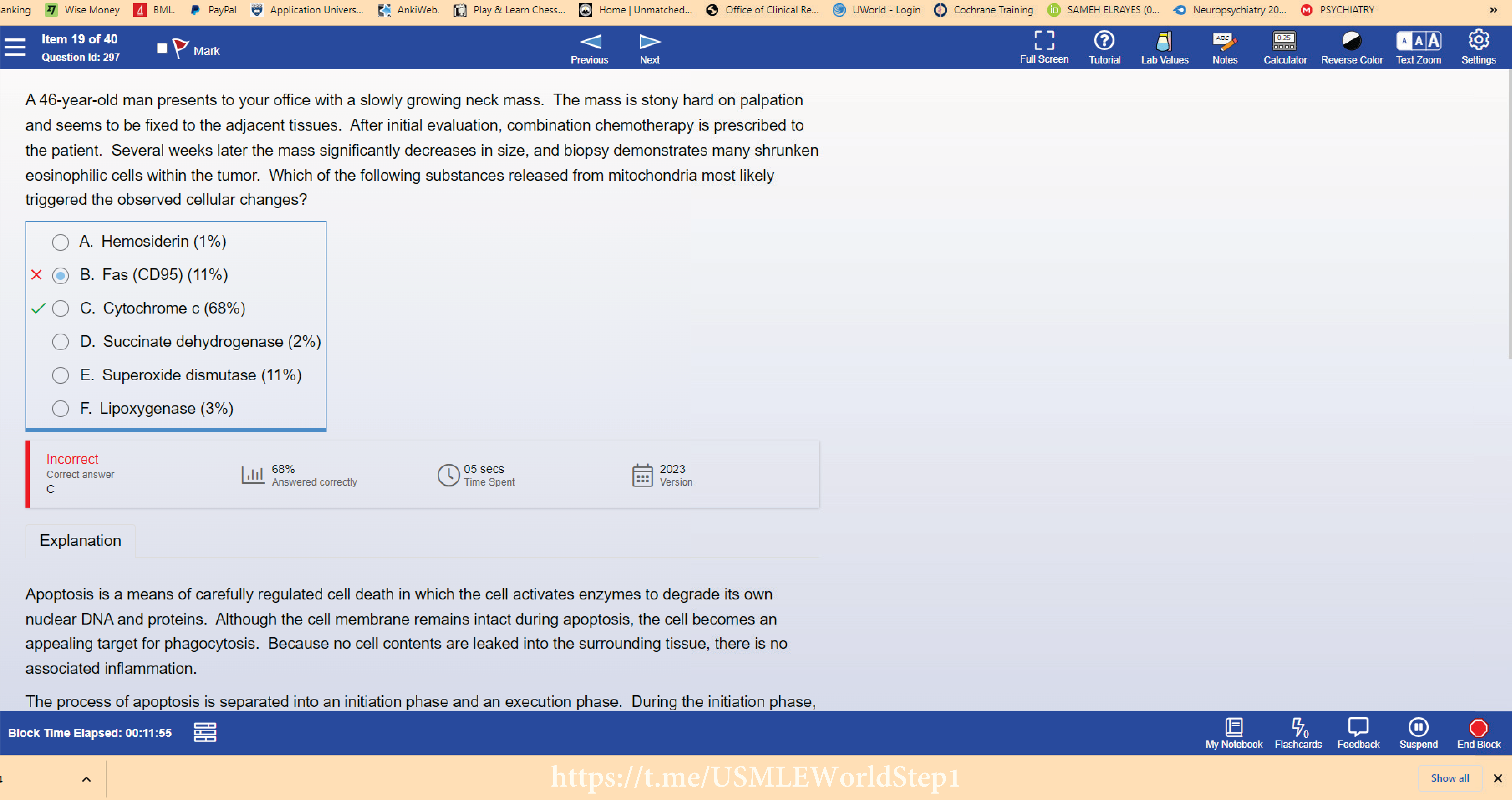
Block Time Elapsed: 00:11:50
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 19 of 40
Question Id: 297
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:50
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 46-year-old man presents to your office with a slowly growing neck mass. The mass is stony hard on palpation and seems to be fixed to the adjacent tissues. After initial evaluation, combination chemotherapy is prescribed to the patient. Several weeks later the mass significantly decreases in size, and biopsy demonstrates many shrunken eosinophilic cells within the tumor. Which of the following substances released from mitochondria most likely triggered the observed cellular changes?

○ A. Hemosiderin
○ B. Fas (CD95)
○ C. Cytochrome c
○ D. Succinate dehydrogenase
○ E. Superoxide dismutase
○ F. Lipoxygenase

Submit


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 19 of 40
Question Id: 297
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 46-year-old man presents to your office with a slowly growing neck mass. The mass is stony hard on palpation and seems to be fixed to the adjacent tissues. After initial evaluation, combination chemotherapy is prescribed to the patient. Several weeks later the mass significantly decreases in size, and biopsy demonstrates many shrunken eosinophilic cells within the tumor. Which of the following substances released from mitochondria most likely triggered the observed cellular changes?

○ A. Hemosiderin (1%)

✗ ● B. Fas (CD95) (11%)

✓ ○ C. Cytochrome c (68%)

○ D. Succinate dehydrogenase (2%)

○ E. Superoxide dismutase (11%)

○ F. Lipoxygenase (3%)

Incorrect
Correct answer
C

68%
Answered correctly

05 secs
Time Spent

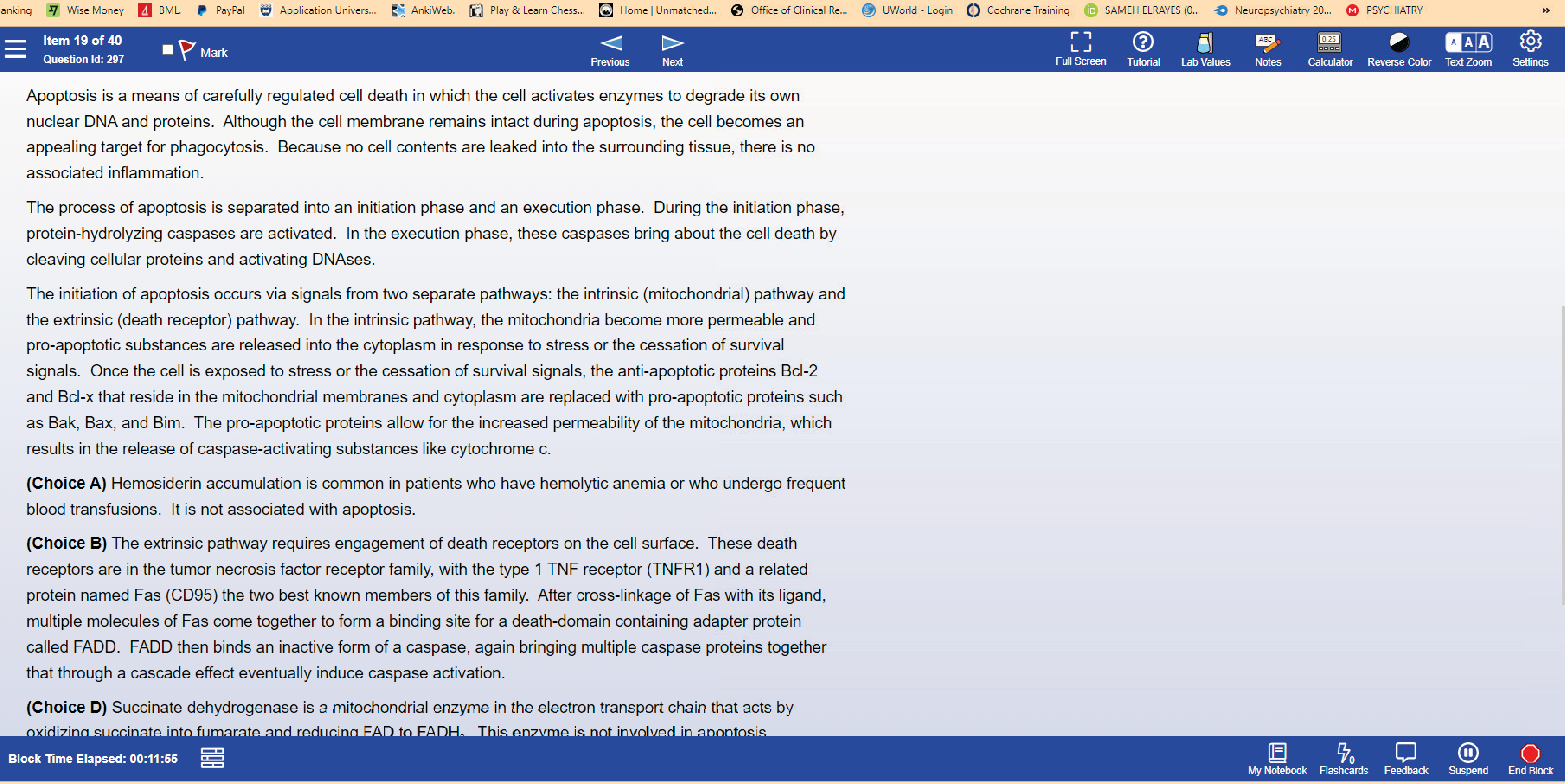
2023
Version

Explanation

Apoptosis is a means of carefully regulated cell death in which the cell activates enzymes to degrade its own nuclear DNA and proteins. Although the cell membrane remains intact during apoptosis, the cell becomes an appealing target for phagocytosis. Because no cell contents are leaked into the surrounding tissue, there is no associated inflammation.

The process of apoptosis is separated into an initiation phase and an execution phase. During the initiation phase,

Block Time Elapsed: 00:11:55
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 19 of 40
Question Id: 297
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:11:55
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Apoptosis is a means of carefully regulated cell death in which the cell activates enzymes to degrade its own nuclear DNA and proteins. Although the cell membrane remains intact during apoptosis, the cell becomes an appealing target for phagocytosis. Because no cell contents are leaked into the surrounding tissue, there is no associated inflammation.

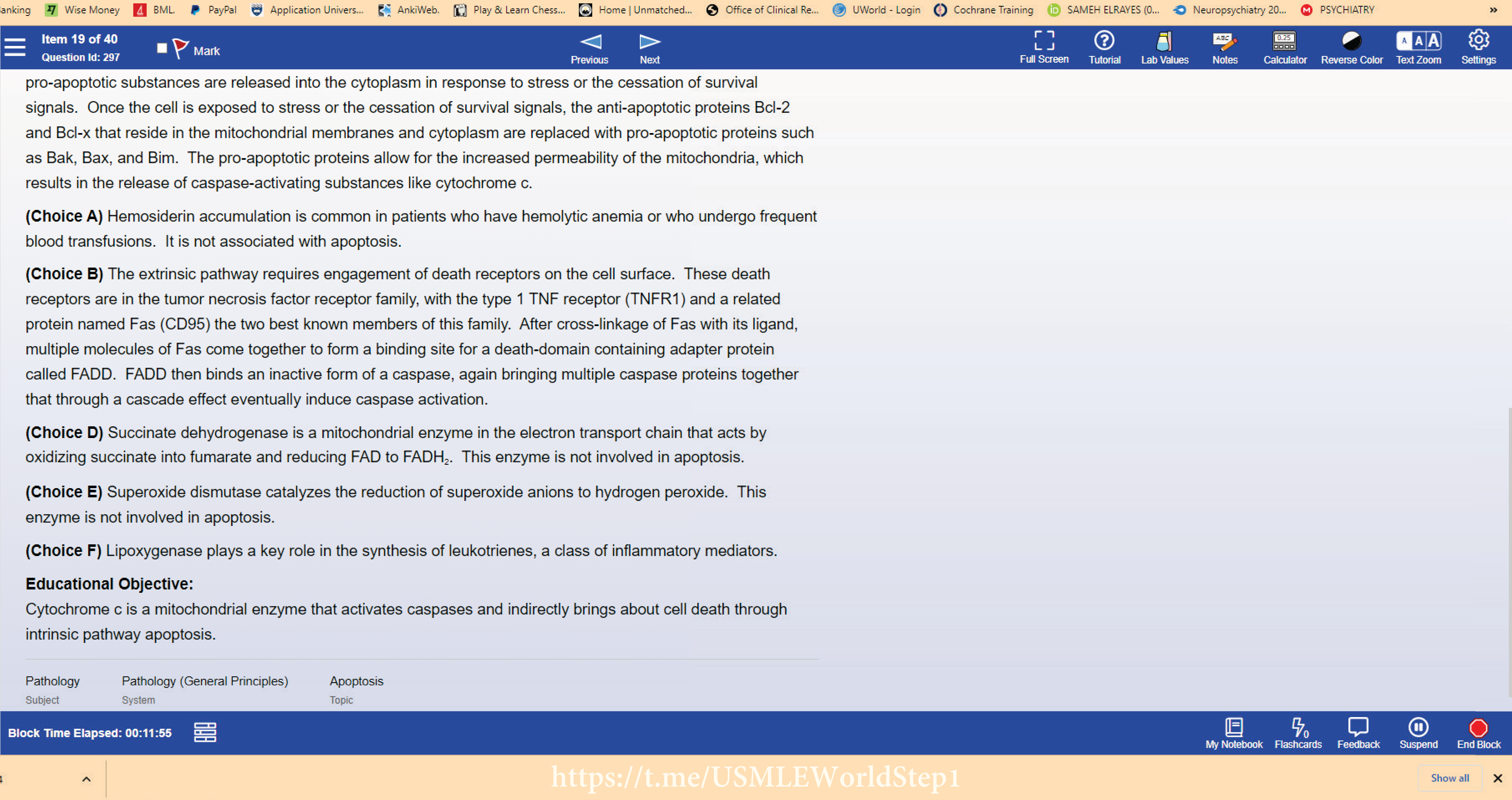
The process of apoptosis is separated into an initiation phase and an execution phase. During the initiation phase, protein-hydrolyzing caspases are activated. In the execution phase, these caspases bring about the cell death by cleaving cellular proteins and activating DNAses.

The initiation of apoptosis occurs via signals from two separate pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway. In the intrinsic pathway, the mitochondria become more permeable and pro-apoptotic substances are released into the cytoplasm in response to stress or the cessation of survival signals. Once the cell is exposed to stress or the cessation of survival signals, the anti-apoptotic proteins Bcl-2 and Bcl-x that reside in the mitochondrial membranes and cytoplasm are replaced with pro-apoptotic proteins such as Bak, Bax, and Bim. The pro-apoptotic proteins allow for the increased permeability of the mitochondria, which results in the release of caspase-activating substances like cytochrome c.

(Choice A) Hemosiderin accumulation is common in patients who have hemolytic anemia or who undergo frequent blood transfusions. It is not associated with apoptosis.

(Choice B) The extrinsic pathway requires engagement of death receptors on the cell surface. These death receptors are in the tumor necrosis factor receptor family, with the type 1 TNF receptor (TNFR1) and a related protein named Fas (CD95) the two best known members of this family. After cross-linkage of Fas with its ligand, multiple molecules of Fas come together to form a binding site for a death-domain containing adapter protein called FADD. FADD then binds an inactive form of a caspase, again bringing multiple caspase proteins together that through a cascade effect eventually induce caspase activation.

(Choice D) Succinate dehydrogenase is a mitochondrial enzyme in the electron transport chain that acts by oxidizing succinate into fumarate and reducing FAD to $FADH_2$. This enzyme is not involved in apoptosis


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 19 of 40
Question Id: 297
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

pro-apoptotic substances are released into the cytoplasm in response to stress or the cessation of survival signals. Once the cell is exposed to stress or the cessation of survival signals, the anti-apoptotic proteins Bcl-2 and Bcl-x that reside in the mitochondrial membranes and cytoplasm are replaced with pro-apoptotic proteins such as Bak, Bax, and Bim. The pro-apoptotic proteins allow for the increased permeability of the mitochondria, which results in the release of caspase-activating substances like cytochrome c.

(Choice A) Hemosiderin accumulation is common in patients who have hemolytic anemia or who undergo frequent blood transfusions. It is not associated with apoptosis.

(Choice B) The extrinsic pathway requires engagement of death receptors on the cell surface. These death receptors are in the tumor necrosis factor receptor family, with the type 1 TNF receptor (TNFR1) and a related protein named Fas (CD95) the two best known members of this family. After cross-linkage of Fas with its ligand, multiple molecules of Fas come together to form a binding site for a death-domain containing adapter protein called FADD. FADD then binds an inactive form of a caspase, again bringing multiple caspase proteins together that through a cascade effect eventually induce caspase activation.

(Choice D) Succinate dehydrogenase is a mitochondrial enzyme in the electron transport chain that acts by oxidizing succinate into fumarate and reducing FAD to $FADH_2$. This enzyme is not involved in apoptosis.

(Choice E) Superoxide dismutase catalyzes the reduction of superoxide anions to hydrogen peroxide. This enzyme is not involved in apoptosis.

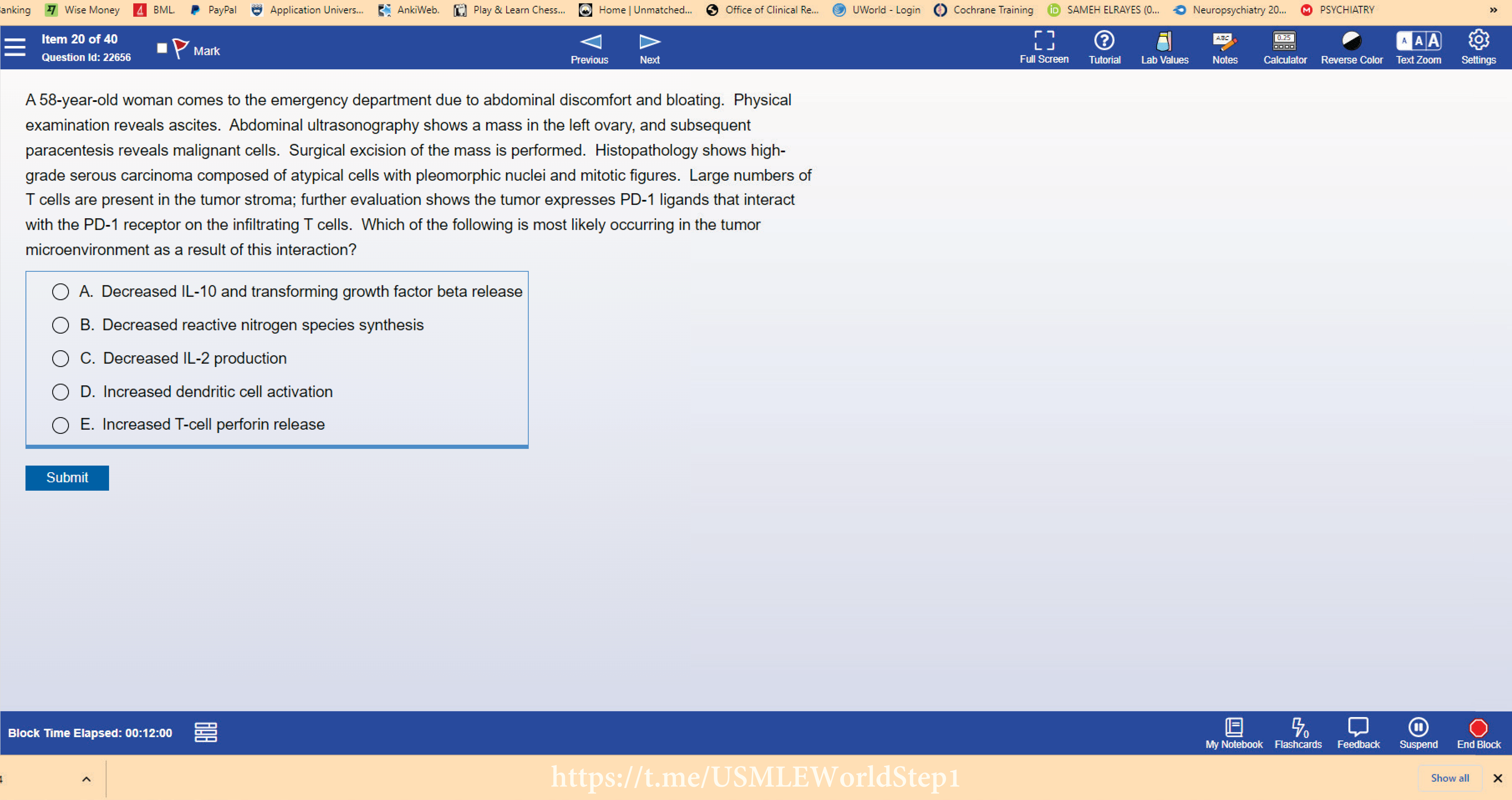
(Choice F) Lipoxygenase plays a key role in the synthesis of leukotrienes, a class of inflammatory mediators.

Educational Objective:

Cytochrome c is a mitochondrial enzyme that activates caspases and indirectly brings about cell death through intrinsic pathway apoptosis.

Pathology	Pathology (General Principles)	Apoptosis
Subject	System	Topic

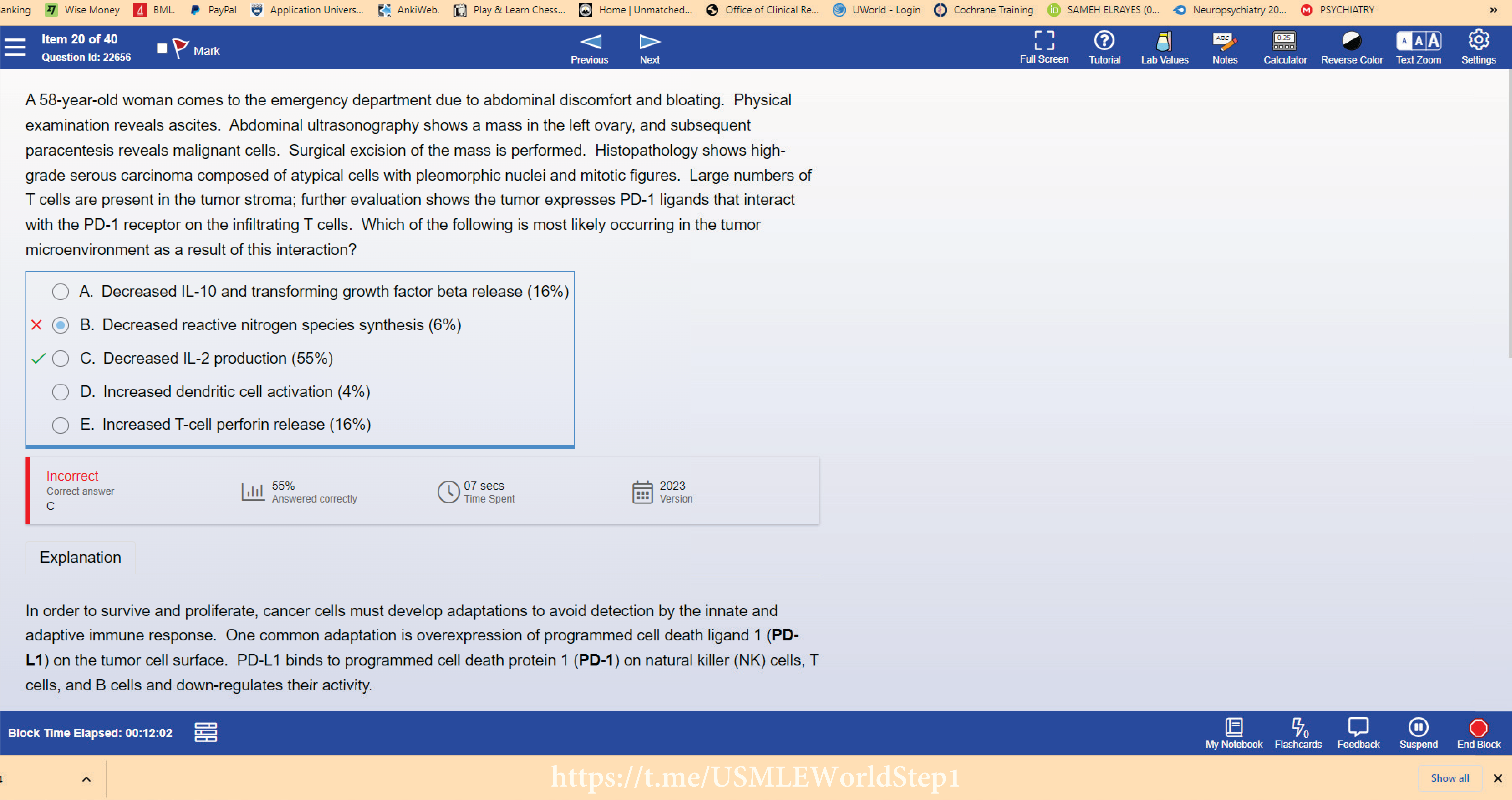
Block Time Elapsed: 00:11:55
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 58-year-old woman comes to the emergency department due to abdominal discomfort and bloating. Physical examination reveals ascites. Abdominal ultrasonography shows a mass in the left ovary, and subsequent paracentesis reveals malignant cells. Surgical excision of the mass is performed. Histopathology shows high-grade serous carcinoma composed of atypical cells with pleomorphic nuclei and mitotic figures. Large numbers of T cells are present in the tumor stroma; further evaluation shows the tumor expresses PD-1 ligands that interact with the PD-1 receptor on the infiltrating T cells. Which of the following is most likely occurring in the tumor microenvironment as a result of this interaction?

- ○ A. Decreased IL-10 and transforming growth factor beta release
- ○ B. Decreased reactive nitrogen species synthesis
- ○ C. Decreased IL-2 production
- ○ D. Increased dendritic cell activation
- ○ E. Increased T-cell perforin release

Submit
Block Time Elapsed: 00:12:00
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 58-year-old woman comes to the emergency department due to abdominal discomfort and bloating. Physical examination reveals ascites. Abdominal ultrasonography shows a mass in the left ovary, and subsequent paracentesis reveals malignant cells. Surgical excision of the mass is performed. Histopathology shows high-grade serous carcinoma composed of atypical cells with pleomorphic nuclei and mitotic figures. Large numbers of T cells are present in the tumor stroma; further evaluation shows the tumor expresses PD-1 ligands that interact with the PD-1 receptor on the infiltrating T cells. Which of the following is most likely occurring in the tumor microenvironment as a result of this interaction?

- ○ A. Decreased IL-10 and transforming growth factor beta release (16%)
- ✗ ● B. Decreased reactive nitrogen species synthesis (6%)
- ✓ ○ C. Decreased IL-2 production (55%)
- ○ D. Increased dendritic cell activation (4%)
- ○ E. Increased T-cell perforin release (16%)

Incorrect
Correct answer
C

55%
Answered correctly

07 secs
Time Spent

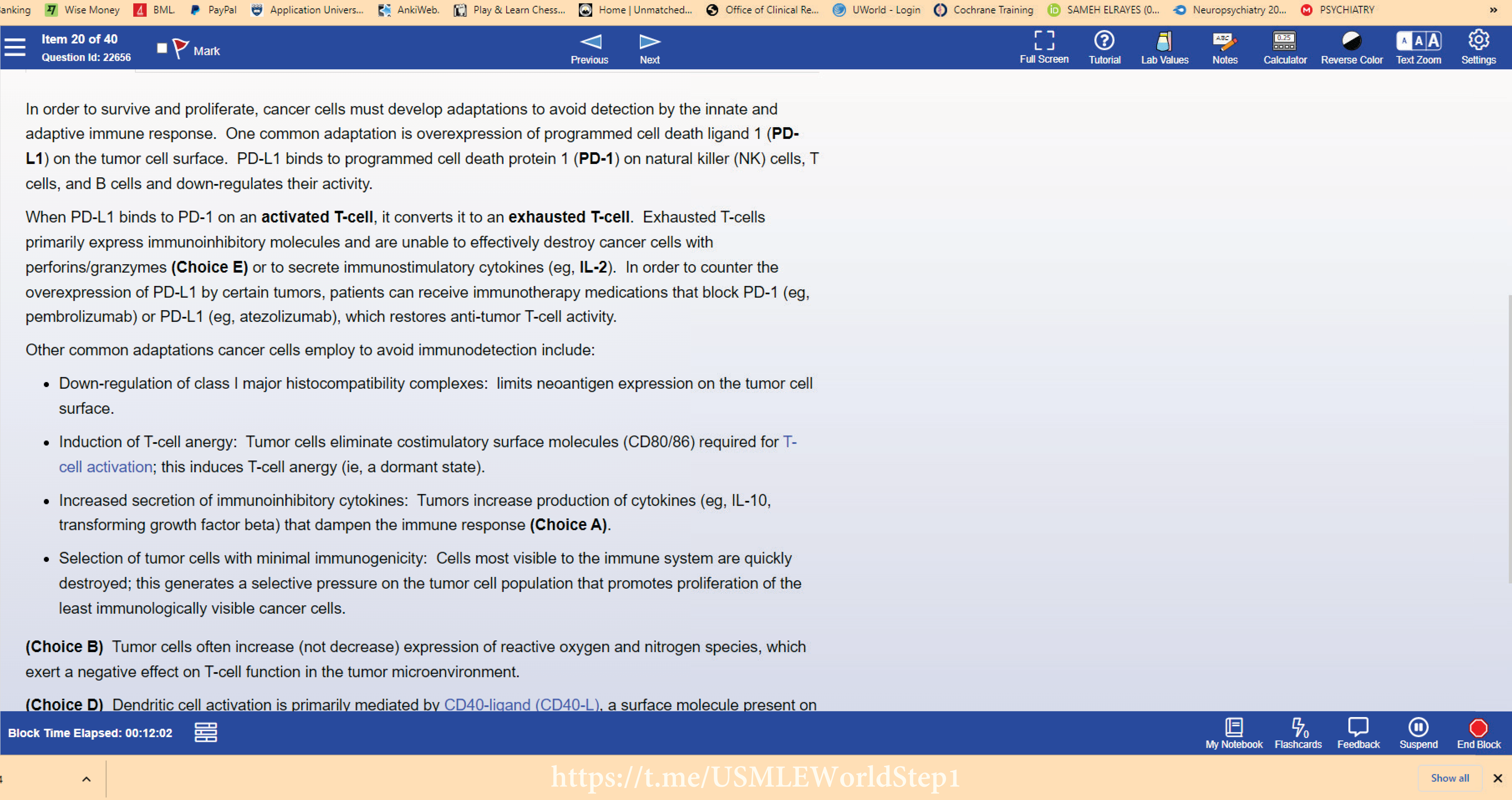
2023
Version

Explanation

In order to survive and proliferate, cancer cells must develop adaptations to avoid detection by the innate and adaptive immune response. One common adaptation is overexpression of programmed cell death ligand 1 (**PD-L1**) on the tumor cell surface. PD-L1 binds to programmed cell death protein 1 (**PD-1**) on natural killer (NK) cells, T cells, and B cells and down-regulates their activity.

Block Time Elapsed: 00:12:02

My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:02
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

In order to survive and proliferate, cancer cells must develop adaptations to avoid detection by the innate and adaptive immune response. One common adaptation is overexpression of programmed cell death ligand 1 (**PD-L1**) on the tumor cell surface. PD-L1 binds to programmed cell death protein 1 (**PD-1**) on natural killer (NK) cells, T cells, and B cells and down-regulates their activity.

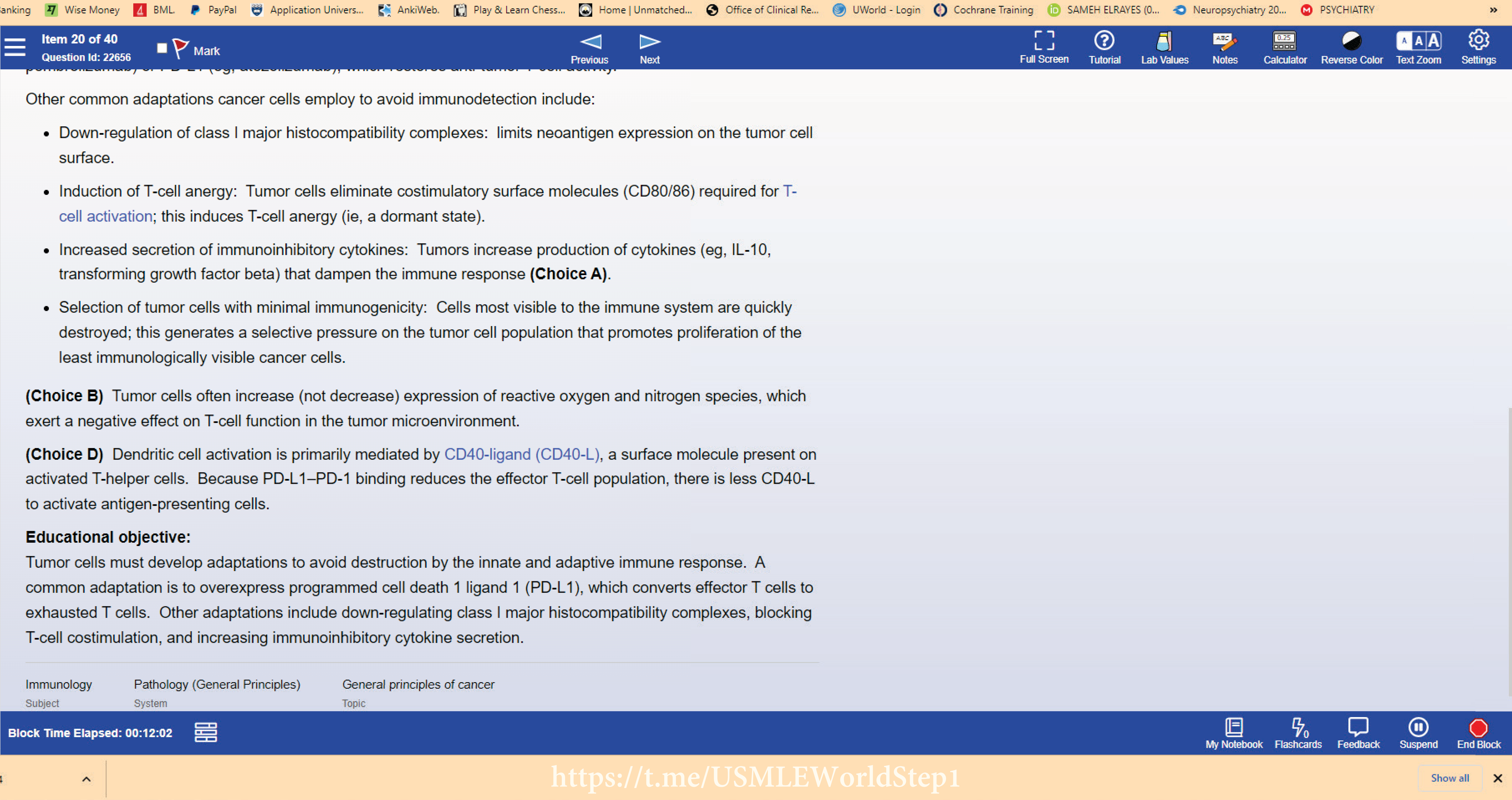
When PD-L1 binds to PD-1 on an **activated T-cell**, it converts it to an **exhausted T-cell**. Exhausted T-cells primarily express immunoinhibitory molecules and are unable to effectively destroy cancer cells with perforins/granzymes **(Choice E)** or to secrete immunostimulatory cytokines (eg, **IL-2**). In order to counter the overexpression of PD-L1 by certain tumors, patients can receive immunotherapy medications that block PD-1 (eg, pembrolizumab) or PD-L1 (eg, atezolizumab), which restores anti-tumor T-cell activity.

Other common adaptations cancer cells employ to avoid immunodetection include:

- Down-regulation of class I major histocompatibility complexes: limits neoantigen expression on the tumor cell surface.
- Induction of T-cell anergy: Tumor cells eliminate costimulatory surface molecules (CD80/86) required for T-cell activation; this induces T-cell anergy (ie, a dormant state).
- Increased secretion of immunoinhibitory cytokines: Tumors increase production of cytokines (eg, IL-10, transforming growth factor beta) that dampen the immune response **(Choice A)**.
- Selection of tumor cells with minimal immunogenicity: Cells most visible to the immune system are quickly destroyed; this generates a selective pressure on the tumor cell population that promotes proliferation of the least immunologically visible cancer cells.

(Choice B) Tumor cells often increase (not decrease) expression of reactive oxygen and nitrogen species, which exert a negative effect on T-cell function in the tumor microenvironment.

(Choice D) Dendritic cell activation is primarily mediated by CD40-ligand (CD40-L), a surface molecule present on


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Other common adaptations cancer cells employ to avoid immunodetection include:

- Down-regulation of class I major histocompatibility complexes: limits neoantigen expression on the tumor cell surface.
- Induction of T-cell anergy: Tumor cells eliminate costimulatory surface molecules (CD80/86) required for T-cell activation; this induces T-cell anergy (ie, a dormant state).
- Increased secretion of immunoinhibitory cytokines: Tumors increase production of cytokines (eg, IL-10, transforming growth factor beta) that dampen the immune response **(Choice A)**.
- Selection of tumor cells with minimal immunogenicity: Cells most visible to the immune system are quickly destroyed; this generates a selective pressure on the tumor cell population that promotes proliferation of the least immunologically visible cancer cells.

(Choice B) Tumor cells often increase (not decrease) expression of reactive oxygen and nitrogen species, which exert a negative effect on T-cell function in the tumor microenvironment.

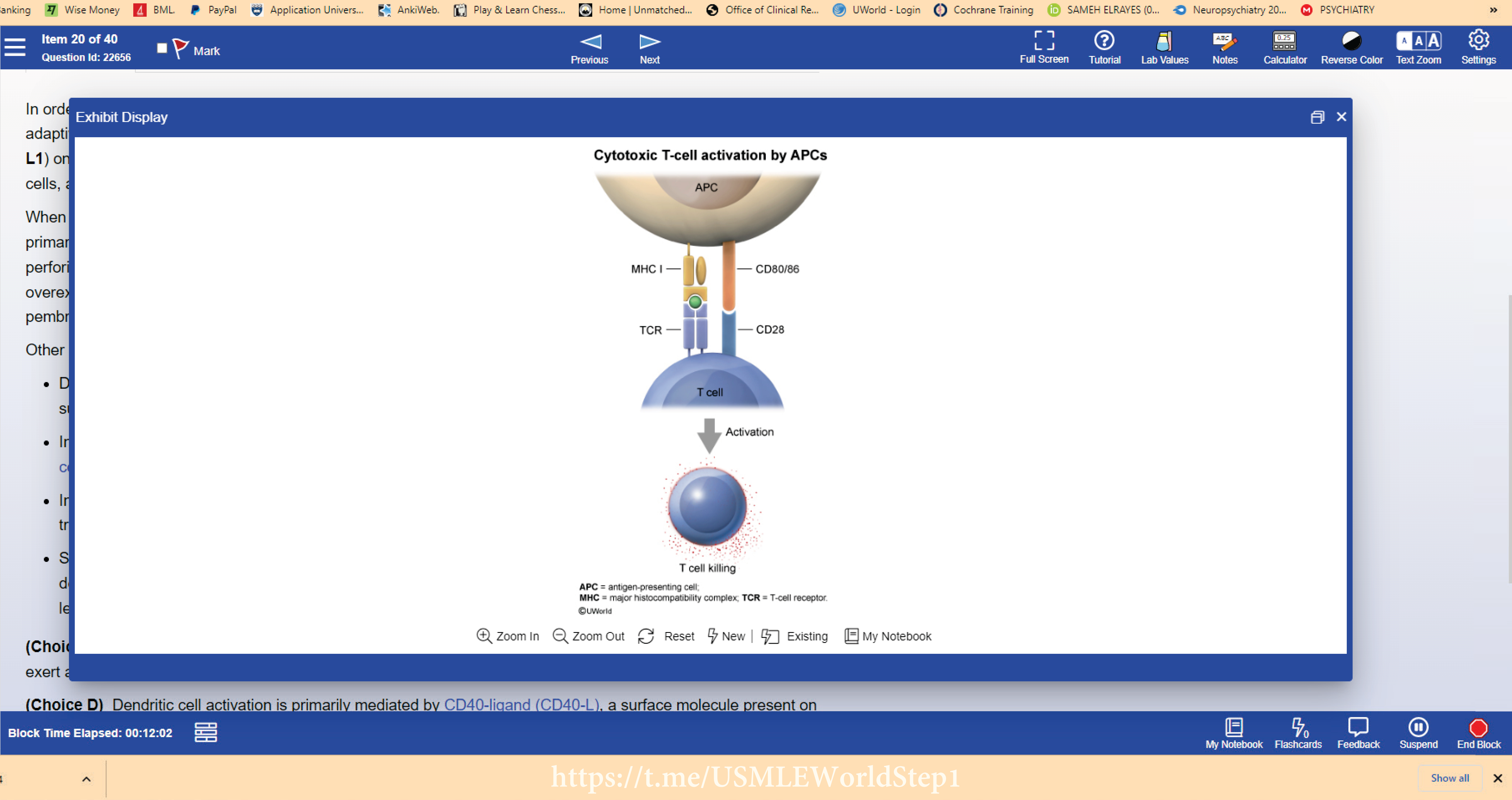
(Choice D) Dendritic cell activation is primarily mediated by CD40-ligand (CD40-L), a surface molecule present on activated T-helper cells. Because PD-L1–PD-1 binding reduces the effector T-cell population, there is less CD40-L to activate antigen-presenting cells.

Educational objective:

Tumor cells must develop adaptations to avoid destruction by the innate and adaptive immune response. A common adaptation is to overexpress programmed cell death 1 ligand 1 (PD-L1), which converts effector T cells to exhausted T cells. Other adaptations include down-regulating class I major histocompatibility complexes, blocking T-cell costimulation, and increasing immunoinhibitory cytokine secretion.

Immunology	Pathology (General Principles)	General principles of cancer
Subject	System	Topic

Block Time Elapsed: 00:12:02
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
APC
MHC I
CD80/86
TCR
CD28
T cell
Activation
T cell killing
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:02
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

In orde

adapti

L1) on

cells, a

When

primar

perfori

overex

pembr

Other

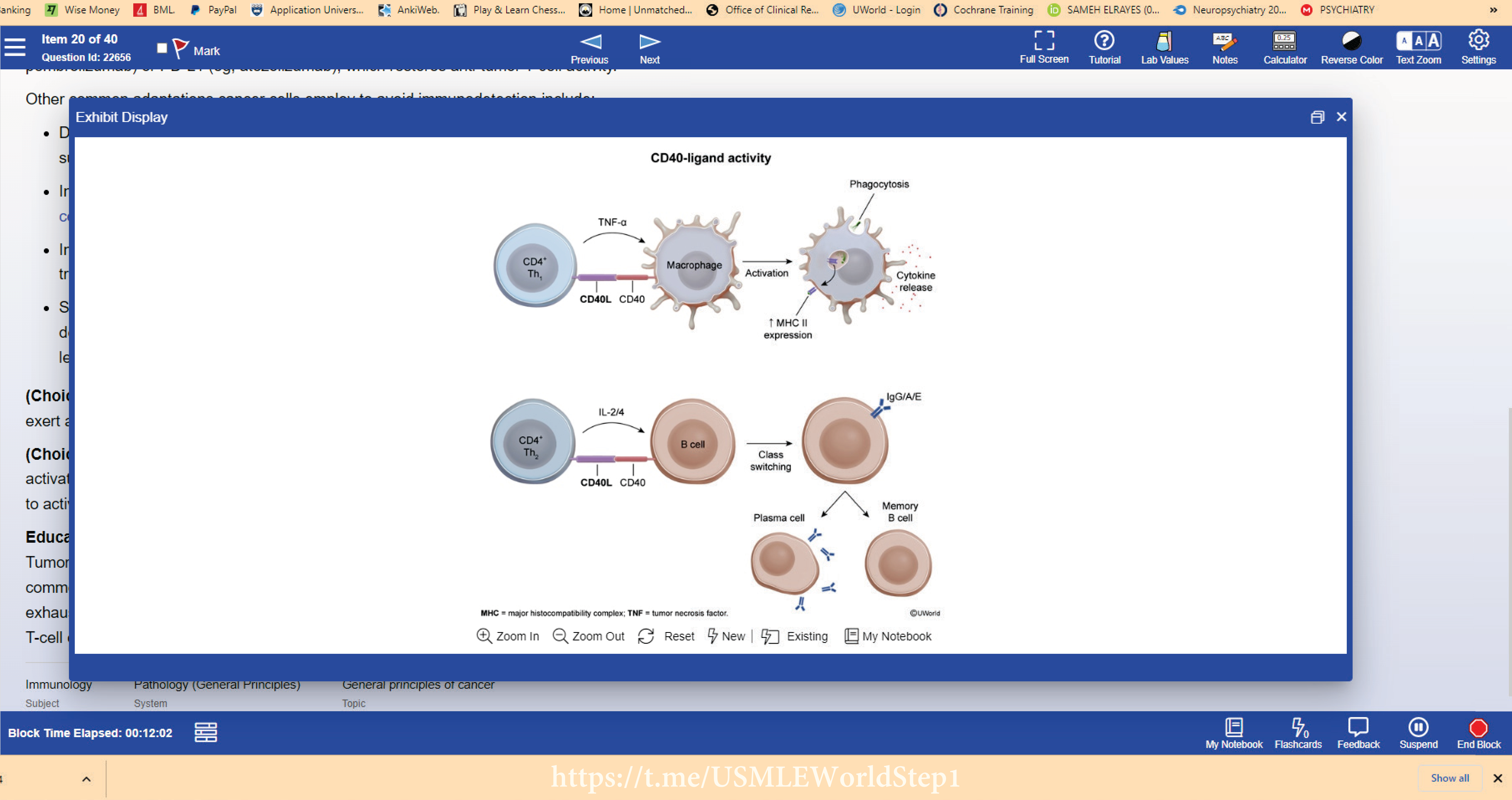
- D
  su
- Ir
  co
- Ir
  tr
- S
  de
  le

(Choic
exert a

(Choice D) Dendritic cell activation is primarily mediated by CD40-ligand (CD40-L), a surface molecule present on

Cytotoxic T-cell activation by APCs

APC = antigen-presenting cell;
MHC = major histocompatibility complex; **TCR** = T-cell receptor.
©UWorld



anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 20 of 40
Question Id: 22656
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Other common adaptations cancer cells employ to avoid immunodetection include:

- D
  su
- In
  c
- In
  tr
- S
  d
  le

(Choi
exert a

(Choi
activat
to acti

Educa
Tumor
comm
exhau
T-cell

Exhibit Display

CD40-ligand activity

CD4+ Th1
TNF-α
Macrophage
CD40L
CD40
Activation
Phagocytosis
Cytokine release
↑ MHC II expression
CD4+ Th2
IL-2/4
B cell
CD40L
CD40
Class switching
IgG/A/E
Plasma cell
Memory B cell

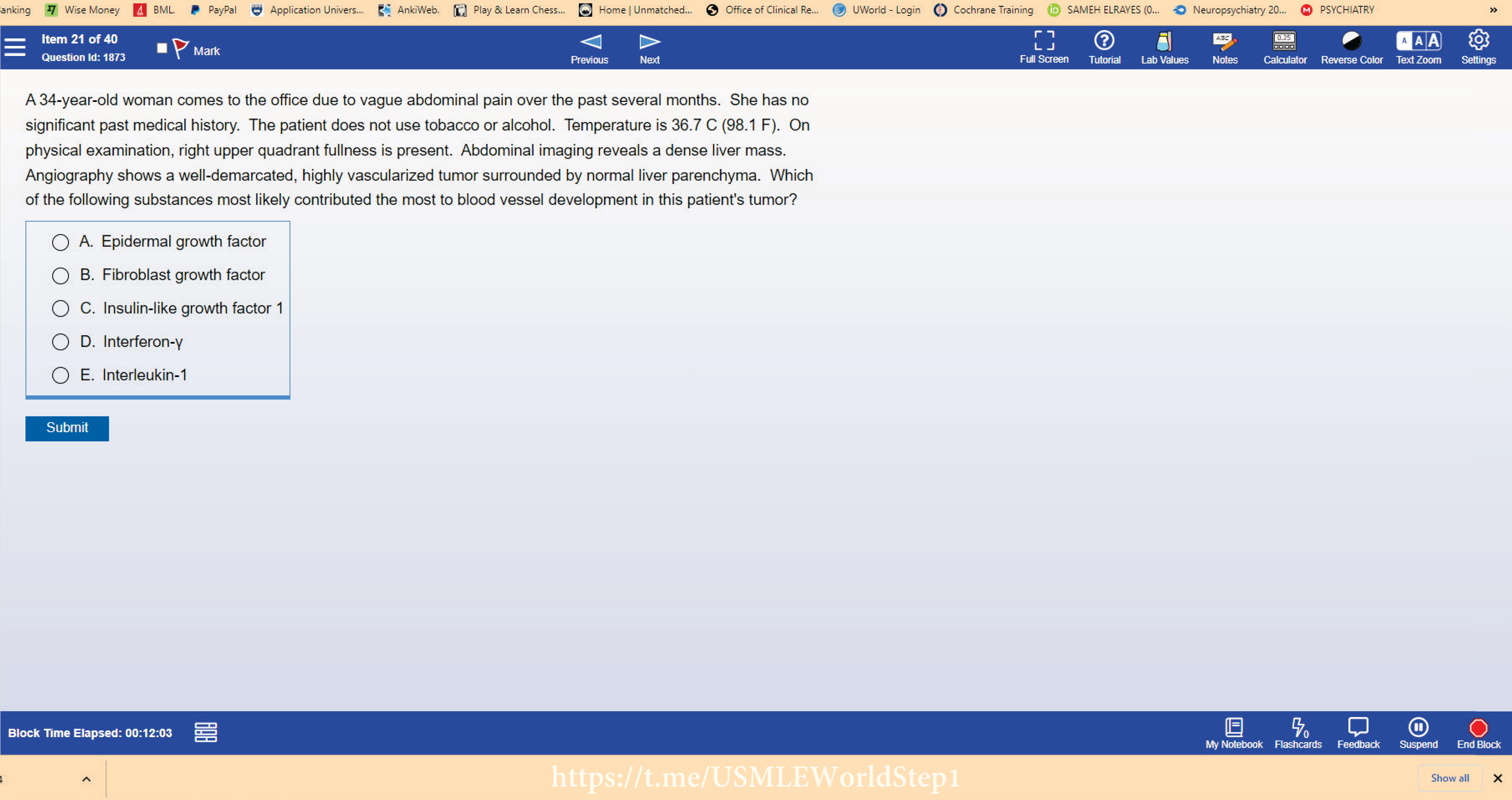
MHC = major histocompatibility complex; TNF = tumor necrosis factor.

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Immunology	Pathology (General Principles)	General principles of cancer
Subject	System	Topic

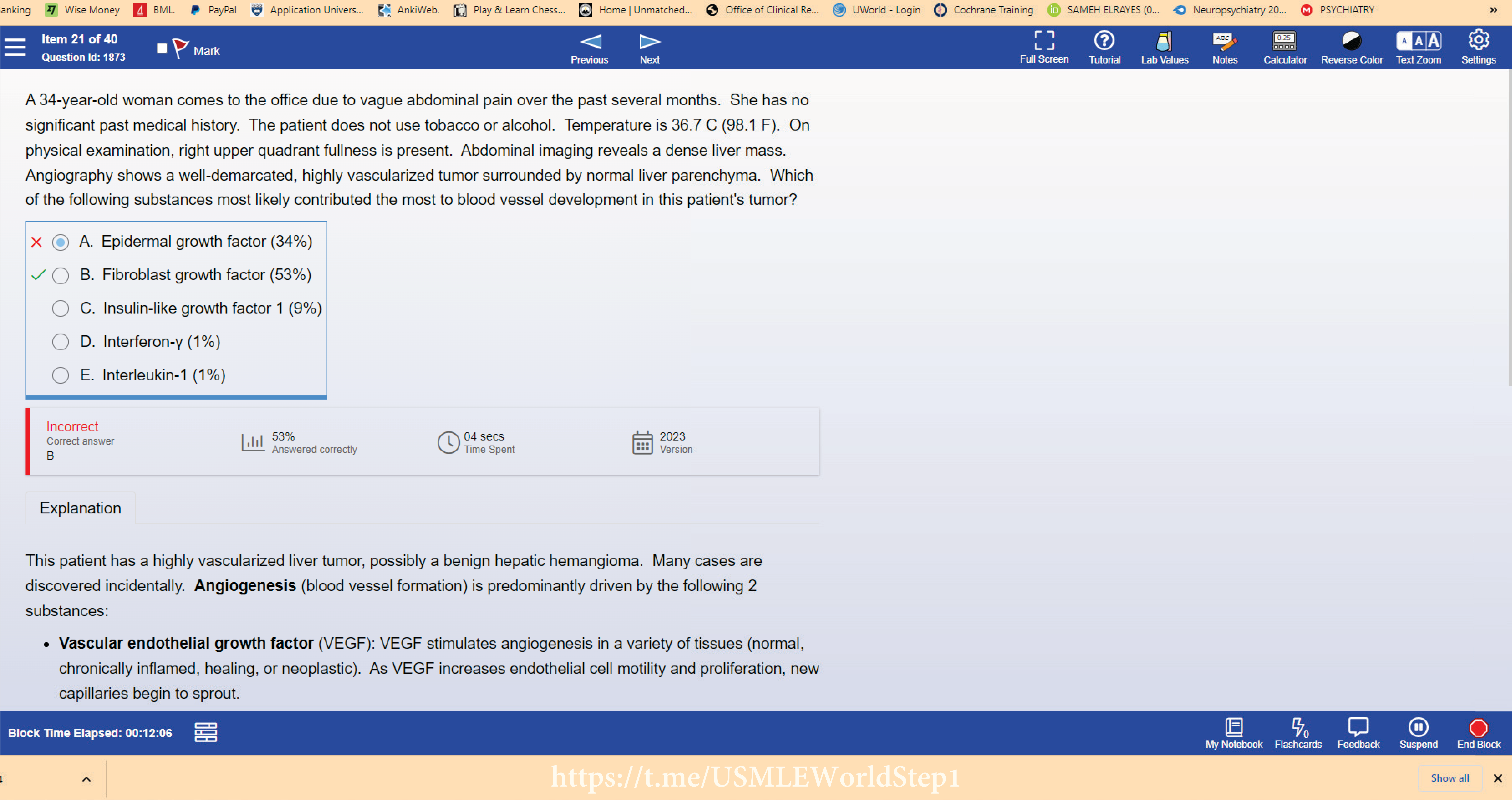
Block Time Elapsed: 00:12:02
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 21 of 40
Question Id: 1873
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:03
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

○ A. Epidermal growth factor
○ B. Fibroblast growth factor
○ C. Insulin-like growth factor 1
○ D. Interferon-γ
○ E. Interleukin-1

Submit


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 21 of 40
Question Id: 1873
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

✗ ● A. Epidermal growth factor (34%)
✓ ○ B. Fibroblast growth factor (53%)
○ C. Insulin-like growth factor 1 (9%)
○ D. Interferon-γ (1%)
○ E. Interleukin-1 (1%)

Incorrect
Correct answer
B

53%
Answered correctly

04 secs
Time Spent

2023
Version

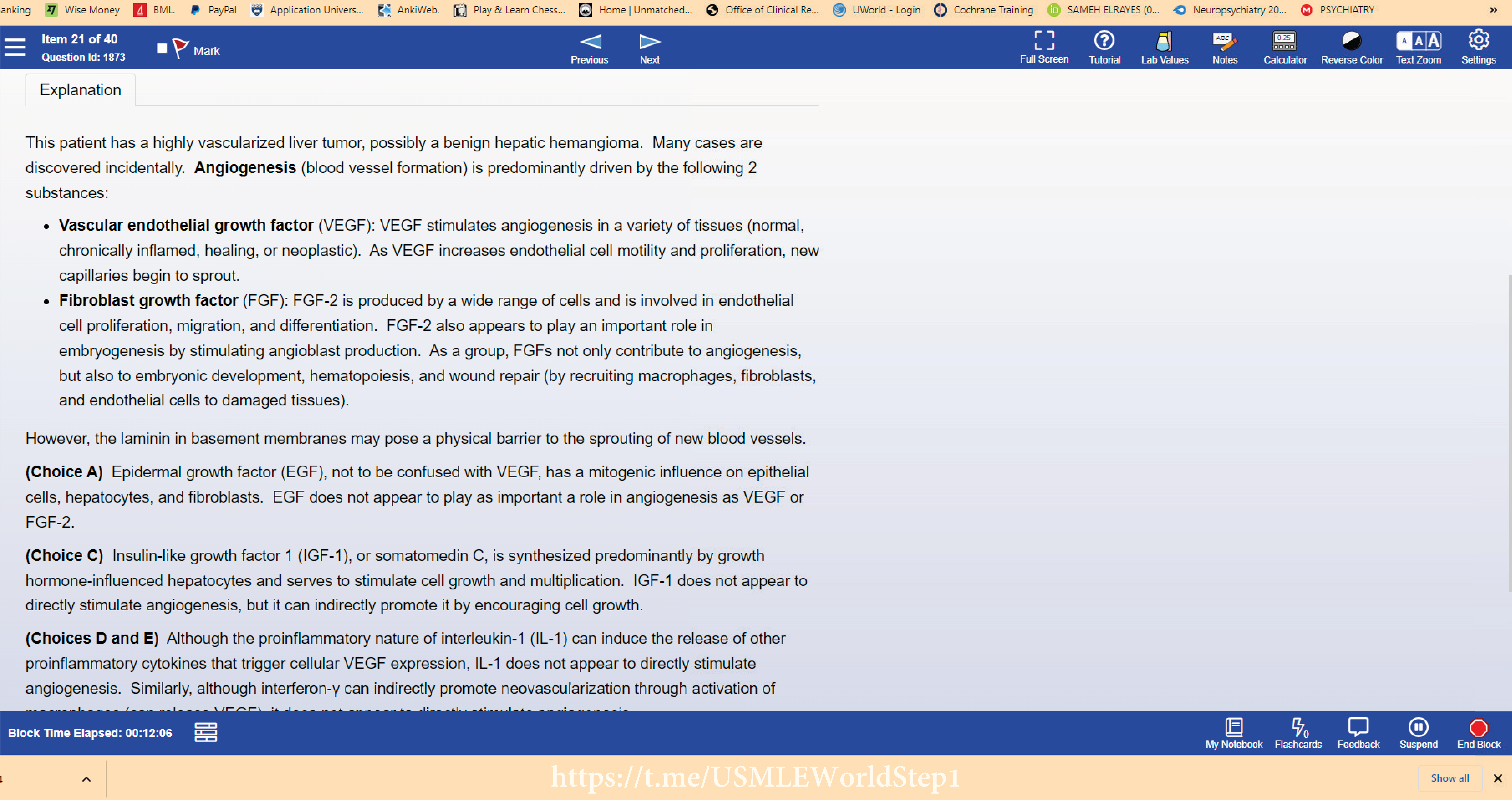
Explanation

This patient has a highly vascularized liver tumor, possibly a benign hepatic hemangioma. Many cases are discovered incidentally. **Angiogenesis** (blood vessel formation) is predominantly driven by the following 2 substances:

- **Vascular endothelial growth factor** (VEGF): VEGF stimulates angiogenesis in a variety of tissues (normal, chronically inflamed, healing, or neoplastic). As VEGF increases endothelial cell motility and proliferation, new capillaries begin to sprout.

Block Time Elapsed: 00:12:06

My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 21 of 40
Question Id: 1873
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:12:06
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

This patient has a highly vascularized liver tumor, possibly a benign hepatic hemangioma. Many cases are discovered incidentally. **Angiogenesis** (blood vessel formation) is predominantly driven by the following 2 substances:

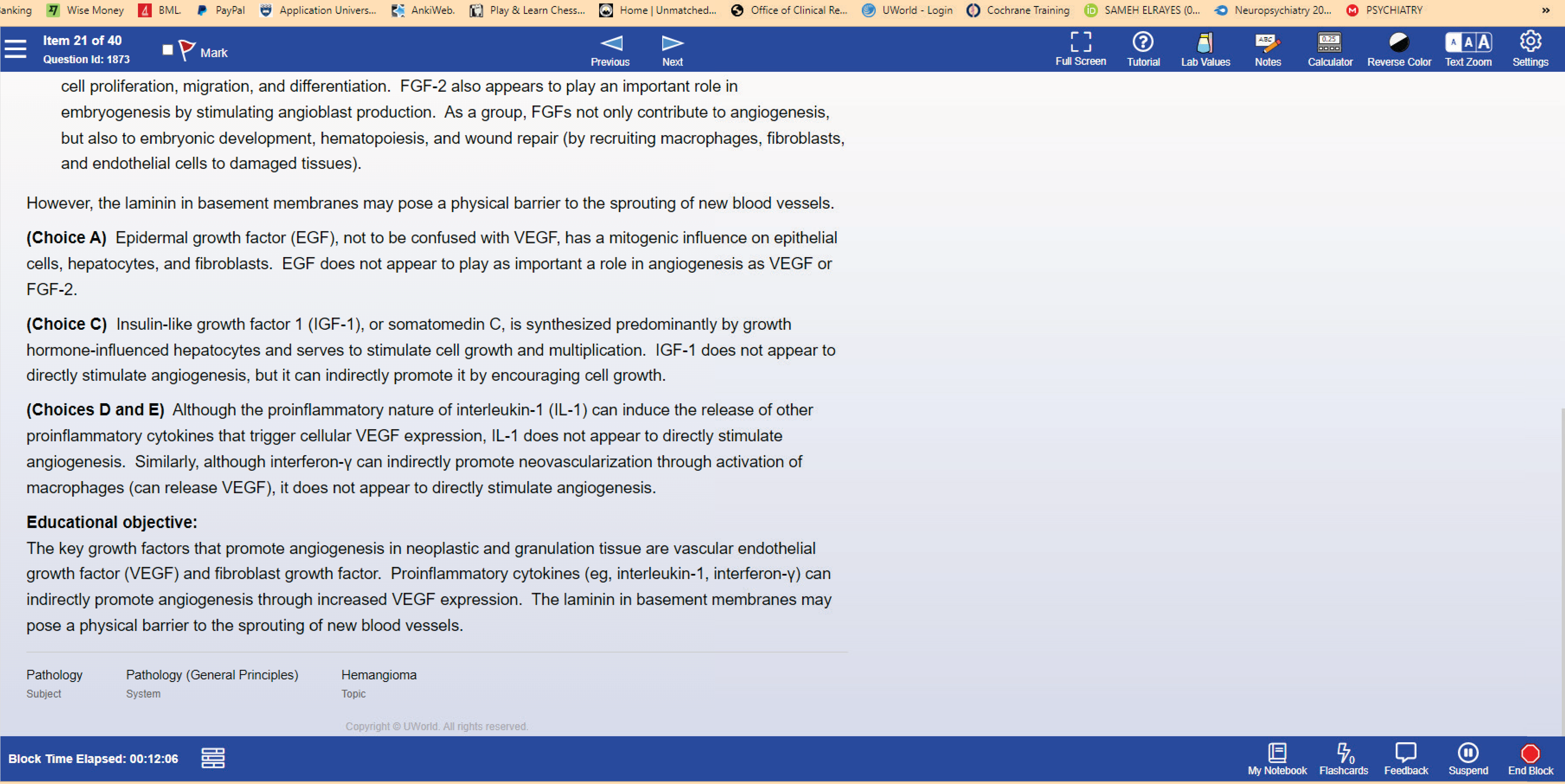
- **Vascular endothelial growth factor** (VEGF): VEGF stimulates angiogenesis in a variety of tissues (normal, chronically inflamed, healing, or neoplastic). As VEGF increases endothelial cell motility and proliferation, new capillaries begin to sprout.
- **Fibroblast growth factor** (FGF): FGF-2 is produced by a wide range of cells and is involved in endothelial cell proliferation, migration, and differentiation. FGF-2 also appears to play an important role in embryogenesis by stimulating angioblast production. As a group, FGFs not only contribute to angiogenesis, but also to embryonic development, hematopoiesis, and wound repair (by recruiting macrophages, fibroblasts, and endothelial cells to damaged tissues).

However, the laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

(Choice A) Epidermal growth factor (EGF), not to be confused with VEGF, has a mitogenic influence on epithelial cells, hepatocytes, and fibroblasts. EGF does not appear to play as important a role in angiogenesis as VEGF or FGF-2.

(Choice C) Insulin-like growth factor 1 (IGF-1), or somatomedin C, is synthesized predominantly by growth hormone-influenced hepatocytes and serves to stimulate cell growth and multiplication. IGF-1 does not appear to directly stimulate angiogenesis, but it can indirectly promote it by encouraging cell growth.

(Choices D and E) Although the proinflammatory nature of interleukin-1 (IL-1) can induce the release of other proinflammatory cytokines that trigger cellular VEGF expression, IL-1 does not appear to directly stimulate angiogenesis. Similarly, although interferon-γ can indirectly promote neovascularization through activation of macrophages (can release VEGF), it does not appear to directly stimulate angiogenesis.


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 21 of 40
Question Id: 1873
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

cell proliferation, migration, and differentiation. FGF-2 also appears to play an important role in embryogenesis by stimulating angioblast production. As a group, FGFs not only contribute to angiogenesis, but also to embryonic development, hematopoiesis, and wound repair (by recruiting macrophages, fibroblasts, and endothelial cells to damaged tissues).

However, the laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

(Choice A) Epidermal growth factor (EGF), not to be confused with VEGF, has a mitogenic influence on epithelial cells, hepatocytes, and fibroblasts. EGF does not appear to play as important a role in angiogenesis as VEGF or FGF-2.

(Choice C) Insulin-like growth factor 1 (IGF-1), or somatomedin C, is synthesized predominantly by growth hormone-influenced hepatocytes and serves to stimulate cell growth and multiplication. IGF-1 does not appear to directly stimulate angiogenesis, but it can indirectly promote it by encouraging cell growth.

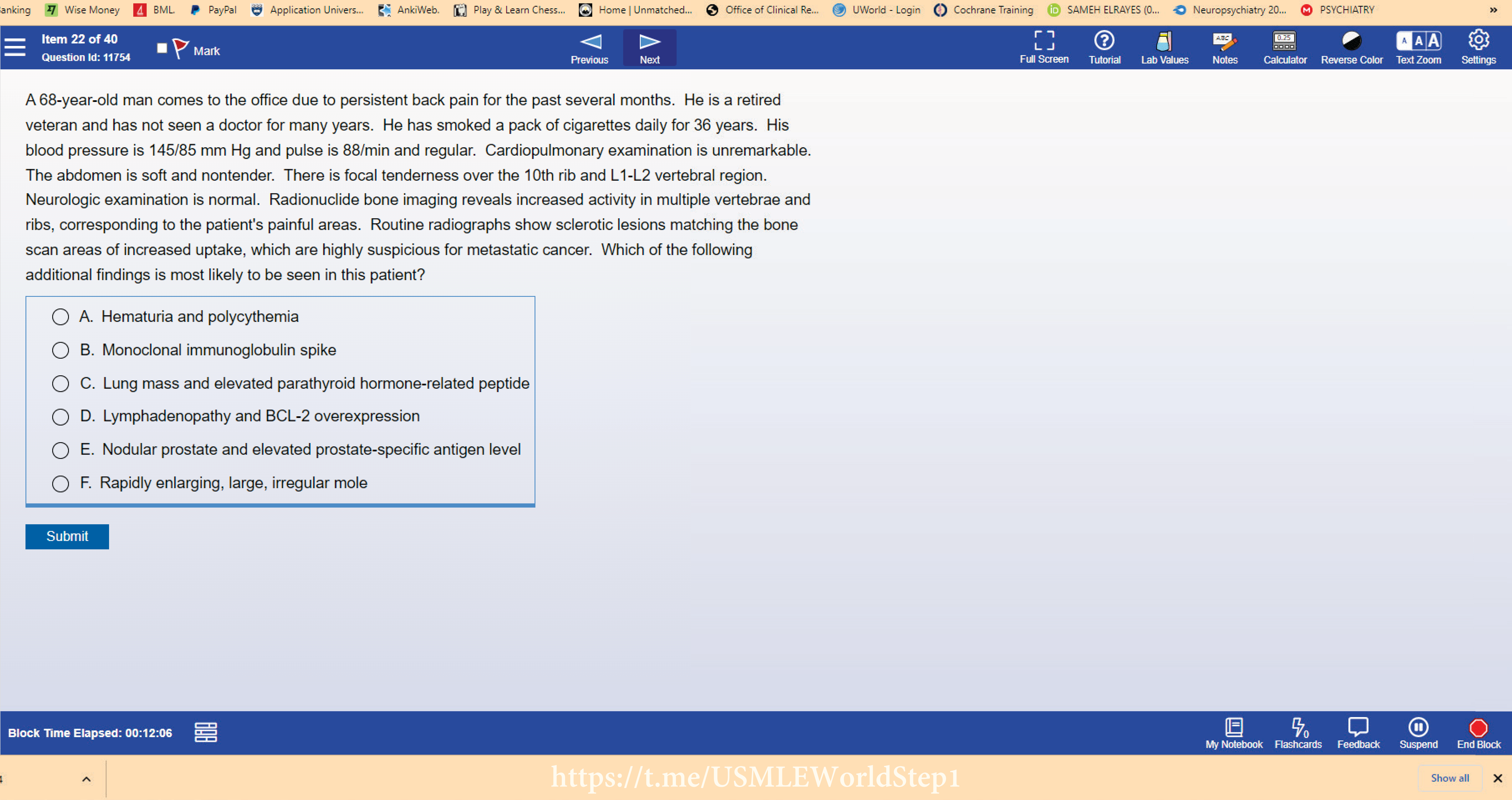
(Choices D and E) Although the proinflammatory nature of interleukin-1 (IL-1) can induce the release of other proinflammatory cytokines that trigger cellular VEGF expression, IL-1 does not appear to directly stimulate angiogenesis. Similarly, although interferon-γ can indirectly promote neovascularization through activation of macrophages (can release VEGF), it does not appear to directly stimulate angiogenesis.

Educational objective:
The key growth factors that promote angiogenesis in neoplastic and granulation tissue are vascular endothelial growth factor (VEGF) and fibroblast growth factor. Proinflammatory cytokines (eg, interleukin-1, interferon-γ) can indirectly promote angiogenesis through increased VEGF expression. The laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

Pathology	Pathology (General Principles)	Hemangioma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

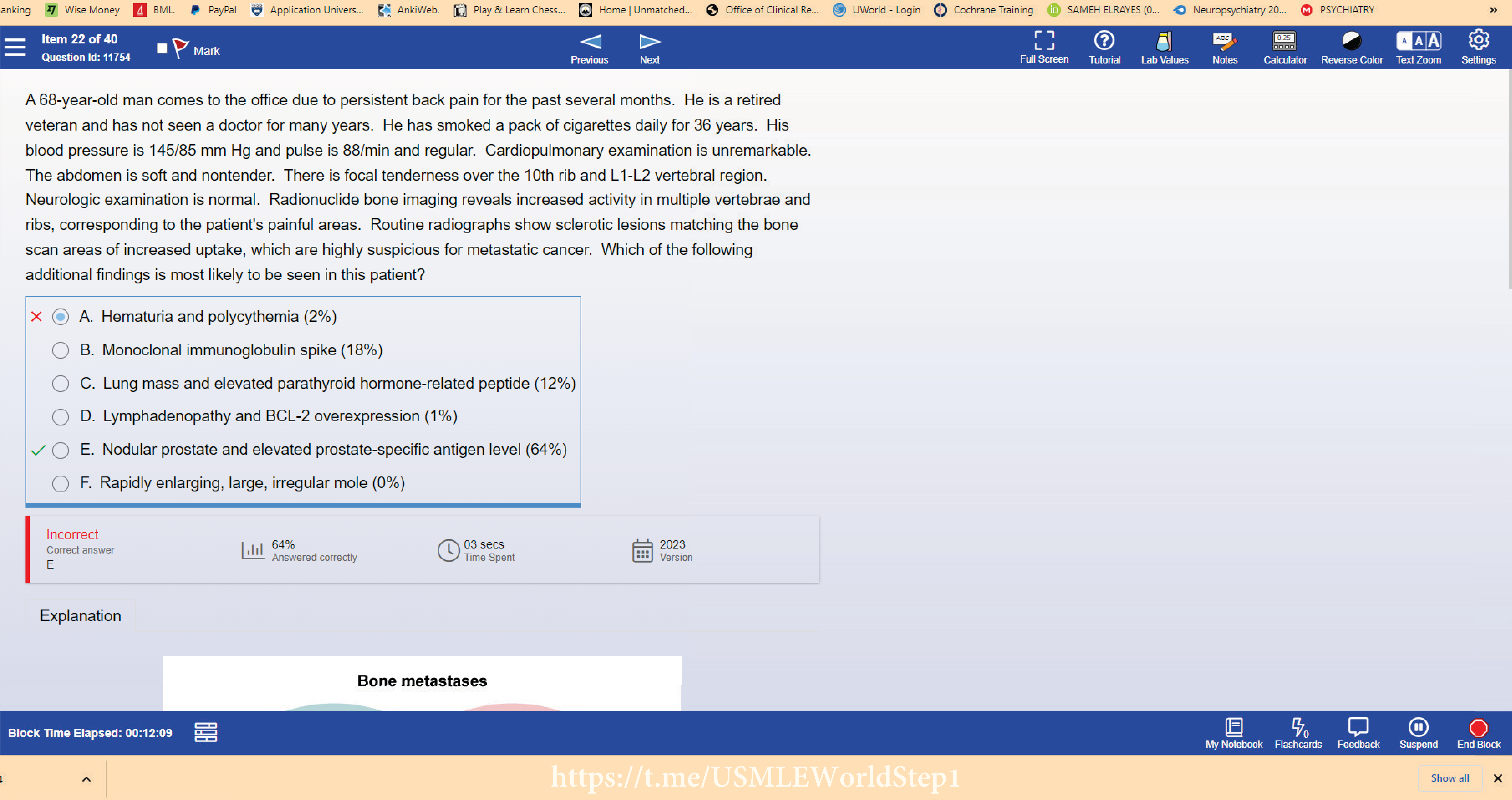
Block Time Elapsed: 00:12:06
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 22 of 40
Question Id: 11754
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 68-year-old man comes to the office due to persistent back pain for the past several months. He is a retired veteran and has not seen a doctor for many years. He has smoked a pack of cigarettes daily for 36 years. His blood pressure is 145/85 mm Hg and pulse is 88/min and regular. Cardiopulmonary examination is unremarkable. The abdomen is soft and nontender. There is focal tenderness over the 10th rib and L1-L2 vertebral region. Neurologic examination is normal. Radionuclide bone imaging reveals increased activity in multiple vertebrae and ribs, corresponding to the patient's painful areas. Routine radiographs show sclerotic lesions matching the bone scan areas of increased uptake, which are highly suspicious for metastatic cancer. Which of the following additional findings is most likely to be seen in this patient?

○ A. Hematuria and polycythemia
○ B. Monoclonal immunoglobulin spike
○ C. Lung mass and elevated parathyroid hormone-related peptide
○ D. Lymphadenopathy and BCL-2 overexpression
○ E. Nodular prostate and elevated prostate-specific antigen level
○ F. Rapidly enlarging, large, irregular mole

Submit
Block Time Elapsed: 00:12:06
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 22 of 40
Question Id: 11754
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 68-year-old man comes to the office due to persistent back pain for the past several months. He is a retired veteran and has not seen a doctor for many years. He has smoked a pack of cigarettes daily for 36 years. His blood pressure is 145/85 mm Hg and pulse is 88/min and regular. Cardiopulmonary examination is unremarkable. The abdomen is soft and nontender. There is focal tenderness over the 10th rib and L1-L2 vertebral region. Neurologic examination is normal. Radionuclide bone imaging reveals increased activity in multiple vertebrae and ribs, corresponding to the patient's painful areas. Routine radiographs show sclerotic lesions matching the bone scan areas of increased uptake, which are highly suspicious for metastatic cancer. Which of the following additional findings is most likely to be seen in this patient?

✗ ● A. Hematuria and polycythemia (2%)

○ B. Monoclonal immunoglobulin spike (18%)

○ C. Lung mass and elevated parathyroid hormone-related peptide (12%)

○ D. Lymphadenopathy and BCL-2 overexpression (1%)

✓ ○ E. Nodular prostate and elevated prostate-specific antigen level (64%)

○ F. Rapidly enlarging, large, irregular mole (0%)

Incorrect
Correct answer
E

64%
Answered correctly

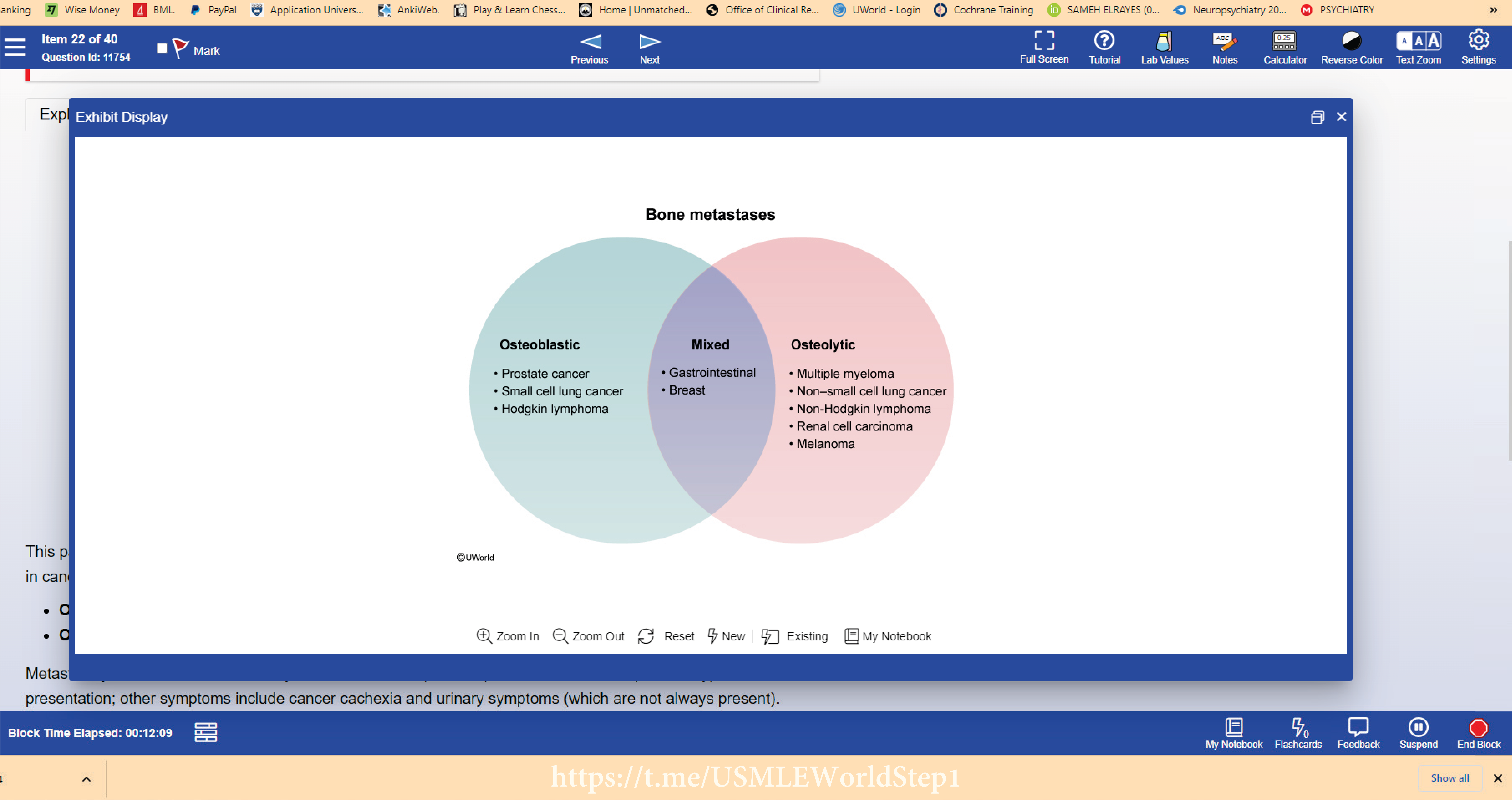
03 secs
Time Spent

2023
Version

Explanation

Bone metastases

Block Time Elapsed: 00:12:09
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 22 of 40
Question Id: 11754
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:09
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Bone metastases

Osteoblastic

- Prostate cancer
- Small cell lung cancer
- Hodgkin lymphoma

Mixed

- Gastrointestinal
- Breast

Osteolytic

- Multiple myeloma
- Non–small cell lung cancer
- Non-Hodgkin lymphoma
- Renal cell carcinoma
- Melanoma

©UWorld

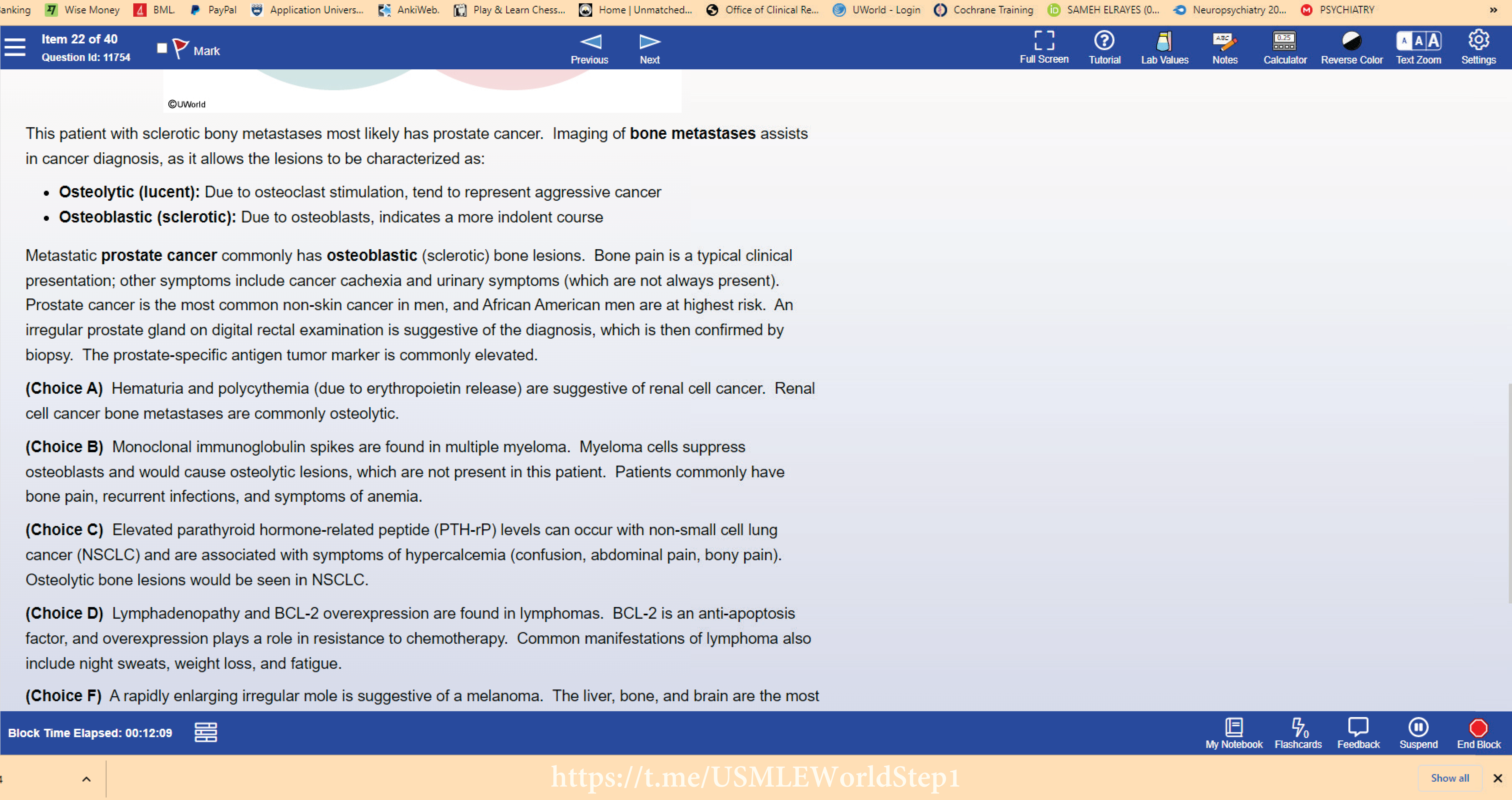
This p

in can

- O
- O

Metas

presentation; other symptoms include cancer cachexia and urinary symptoms (which are not always present).


Item 22 of 40
Question Id: 11754
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Block Time Elapsed: 00:12:09
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

This patient with sclerotic bony metastases most likely has prostate cancer. Imaging of **bone metastases** assists in cancer diagnosis, as it allows the lesions to be characterized as:

- **Osteolytic (lucent):** Due to osteoclast stimulation, tend to represent aggressive cancer
- **Osteoblastic (sclerotic):** Due to osteoblasts, indicates a more indolent course

Metastatic **prostate cancer** commonly has **osteoblastic** (sclerotic) bone lesions. Bone pain is a typical clinical presentation; other symptoms include cancer cachexia and urinary symptoms (which are not always present). Prostate cancer is the most common non-skin cancer in men, and African American men are at highest risk. An irregular prostate gland on digital rectal examination is suggestive of the diagnosis, which is then confirmed by biopsy. The prostate-specific antigen tumor marker is commonly elevated.

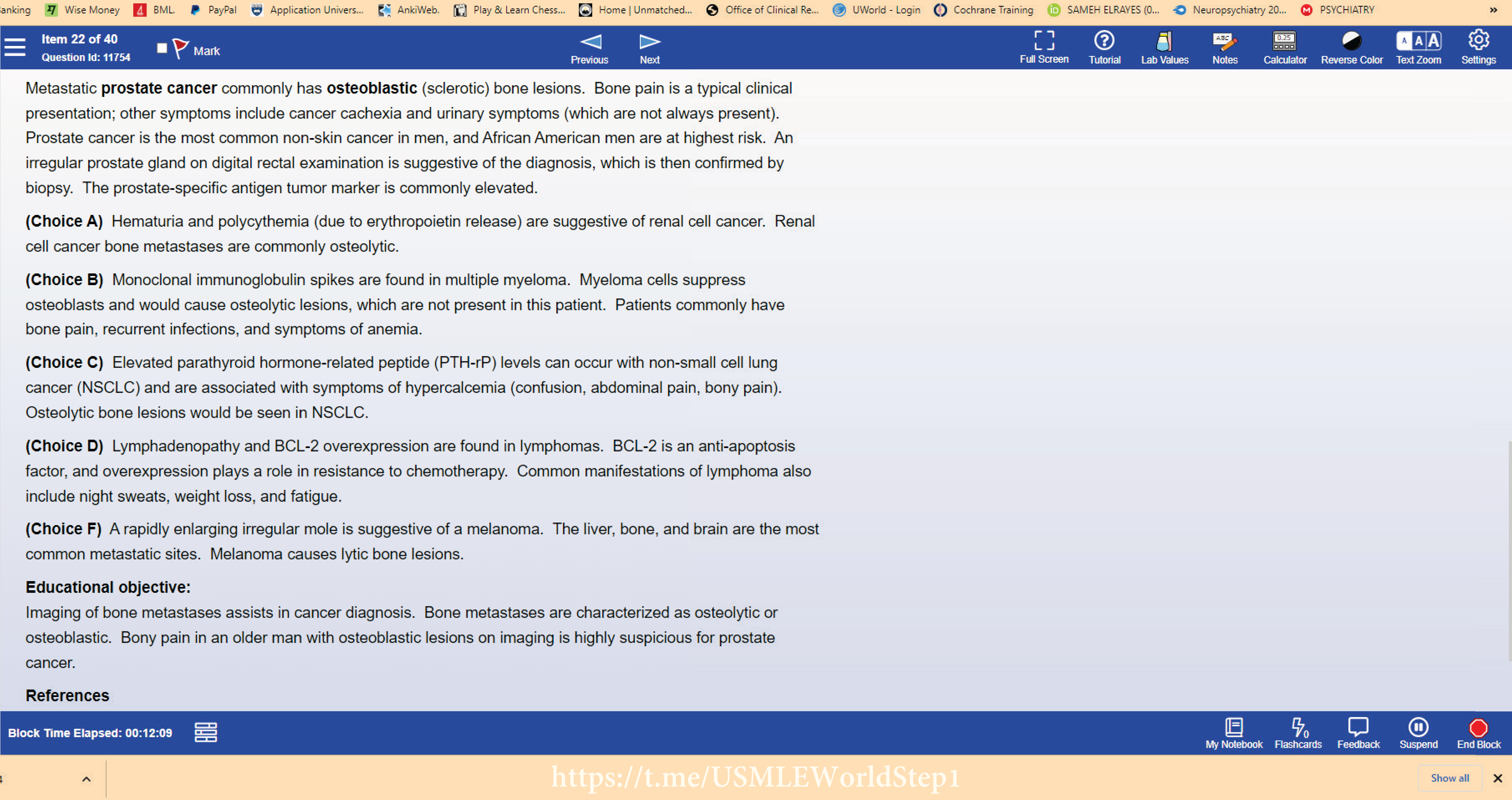
(Choice A) Hematuria and polycythemia (due to erythropoietin release) are suggestive of renal cell cancer. Renal cell cancer bone metastases are commonly osteolytic.

(Choice B) Monoclonal immunoglobulin spikes are found in multiple myeloma. Myeloma cells suppress osteoblasts and would cause osteolytic lesions, which are not present in this patient. Patients commonly have bone pain, recurrent infections, and symptoms of anemia.

(Choice C) Elevated parathyroid hormone-related peptide (PTH-rP) levels can occur with non-small cell lung cancer (NSCLC) and are associated with symptoms of hypercalcemia (confusion, abdominal pain, bony pain). Osteolytic bone lesions would be seen in NSCLC.

(Choice D) Lymphadenopathy and BCL-2 overexpression are found in lymphomas. BCL-2 is an anti-apoptosis factor, and overexpression plays a role in resistance to chemotherapy. Common manifestations of lymphoma also include night sweats, weight loss, and fatigue.

(Choice F) A rapidly enlarging irregular mole is suggestive of a melanoma. The liver, bone, and brain are the most


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 22 of 40
Question Id: 11754

Metastatic **prostate cancer** commonly has **osteoblastic** (sclerotic) bone lesions. Bone pain is a typical clinical presentation; other symptoms include cancer cachexia and urinary symptoms (which are not always present). Prostate cancer is the most common non-skin cancer in men, and African American men are at highest risk. An irregular prostate gland on digital rectal examination is suggestive of the diagnosis, which is then confirmed by biopsy. The prostate-specific antigen tumor marker is commonly elevated.

(Choice A) Hematuria and polycythemia (due to erythropoietin release) are suggestive of renal cell cancer. Renal cell cancer bone metastases are commonly osteolytic.

(Choice B) Monoclonal immunoglobulin spikes are found in multiple myeloma. Myeloma cells suppress osteoblasts and would cause osteolytic lesions, which are not present in this patient. Patients commonly have bone pain, recurrent infections, and symptoms of anemia.

(Choice C) Elevated parathyroid hormone-related peptide (PTH-rP) levels can occur with non-small cell lung cancer (NSCLC) and are associated with symptoms of hypercalcemia (confusion, abdominal pain, bony pain). Osteolytic bone lesions would be seen in NSCLC.

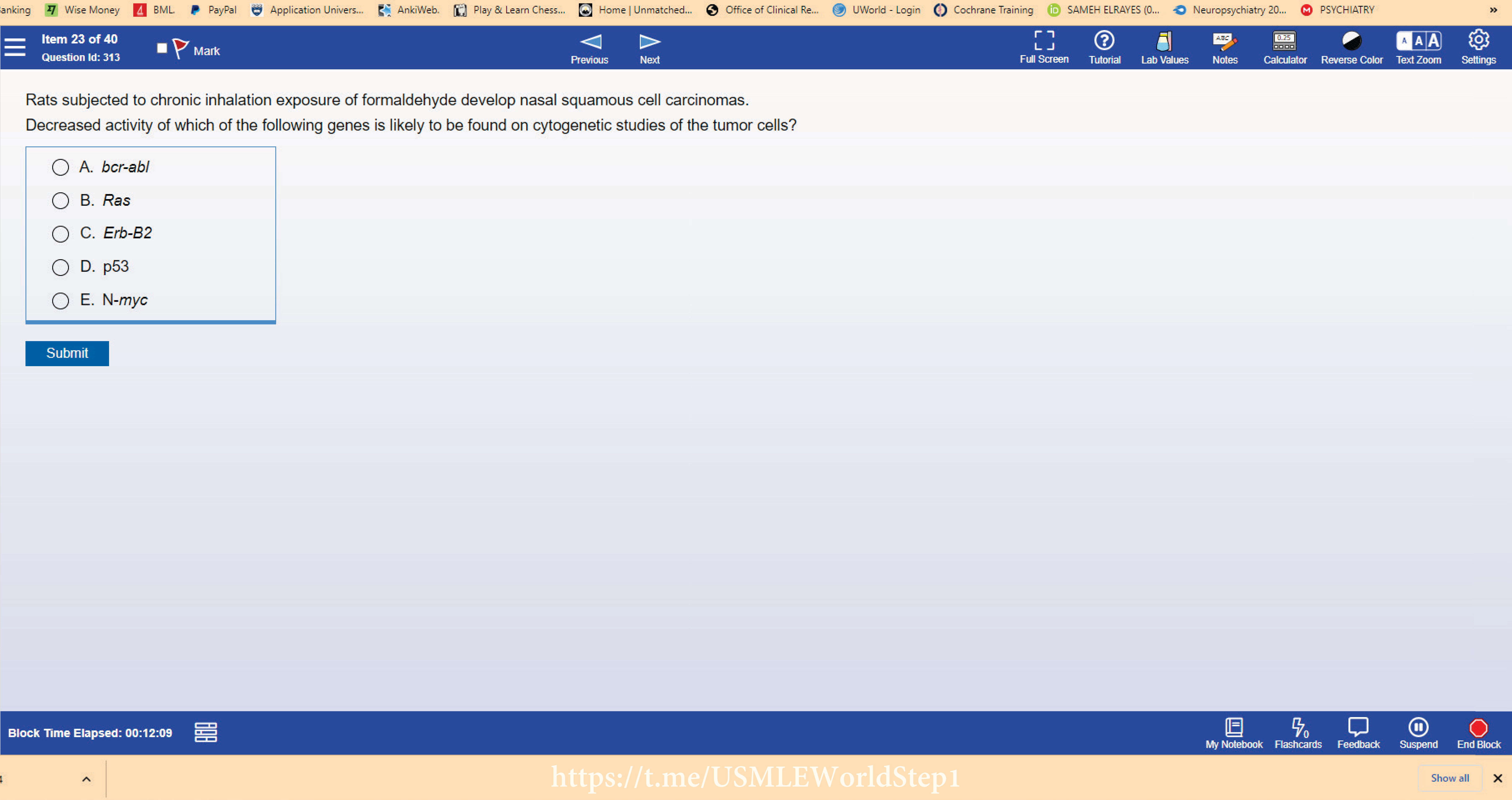
(Choice D) Lymphadenopathy and BCL-2 overexpression are found in lymphomas. BCL-2 is an anti-apoptosis factor, and overexpression plays a role in resistance to chemotherapy. Common manifestations of lymphoma also include night sweats, weight loss, and fatigue.

(Choice F) A rapidly enlarging irregular mole is suggestive of a melanoma. The liver, bone, and brain are the most common metastatic sites. Melanoma causes lytic bone lesions.

Educational objective:
Imaging of bone metastases assists in cancer diagnosis. Bone metastases are characterized as osteolytic or osteoblastic. Bony pain in an older man with osteoblastic lesions on imaging is highly suspicious for prostate cancer.

References

Block Time Elapsed: 00:12:09

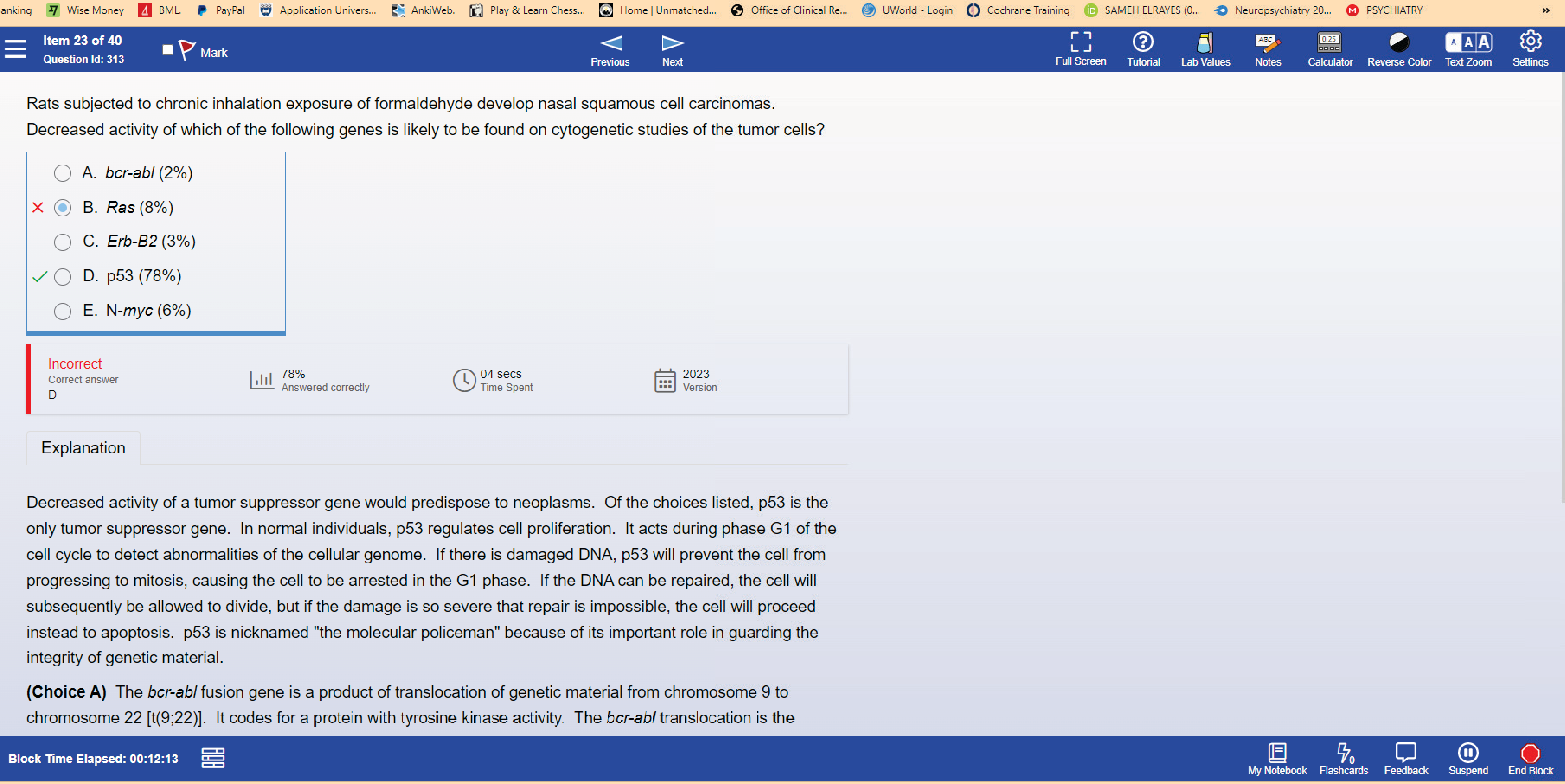

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 23 of 40
Question Id: 313
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Rats subjected to chronic inhalation exposure of formaldehyde develop nasal squamous cell carcinomas.

Decreased activity of which of the following genes is likely to be found on cytogenetic studies of the tumor cells?

○ A. *bcr-abl*
○ B. *Ras*
○ C. *Erb-B2*
○ D. p53
○ E. N-*myc*

Submit
Block Time Elapsed: 00:12:09
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Item 23 of 40
Question Id: 313
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:13
My Notebook
Flashcards
Feedback
Suspend
End Block

Rats subjected to chronic inhalation exposure of formaldehyde develop nasal squamous cell carcinomas. Decreased activity of which of the following genes is likely to be found on cytogenetic studies of the tumor cells?

○ A. *bcr-abl* (2%)
✗ ● B. *Ras* (8%)
○ C. *Erb-B2* (3%)
✓ ○ D. p53 (78%)
○ E. N-*myc* (6%)

Incorrect
Correct answer
D

78%
Answered correctly

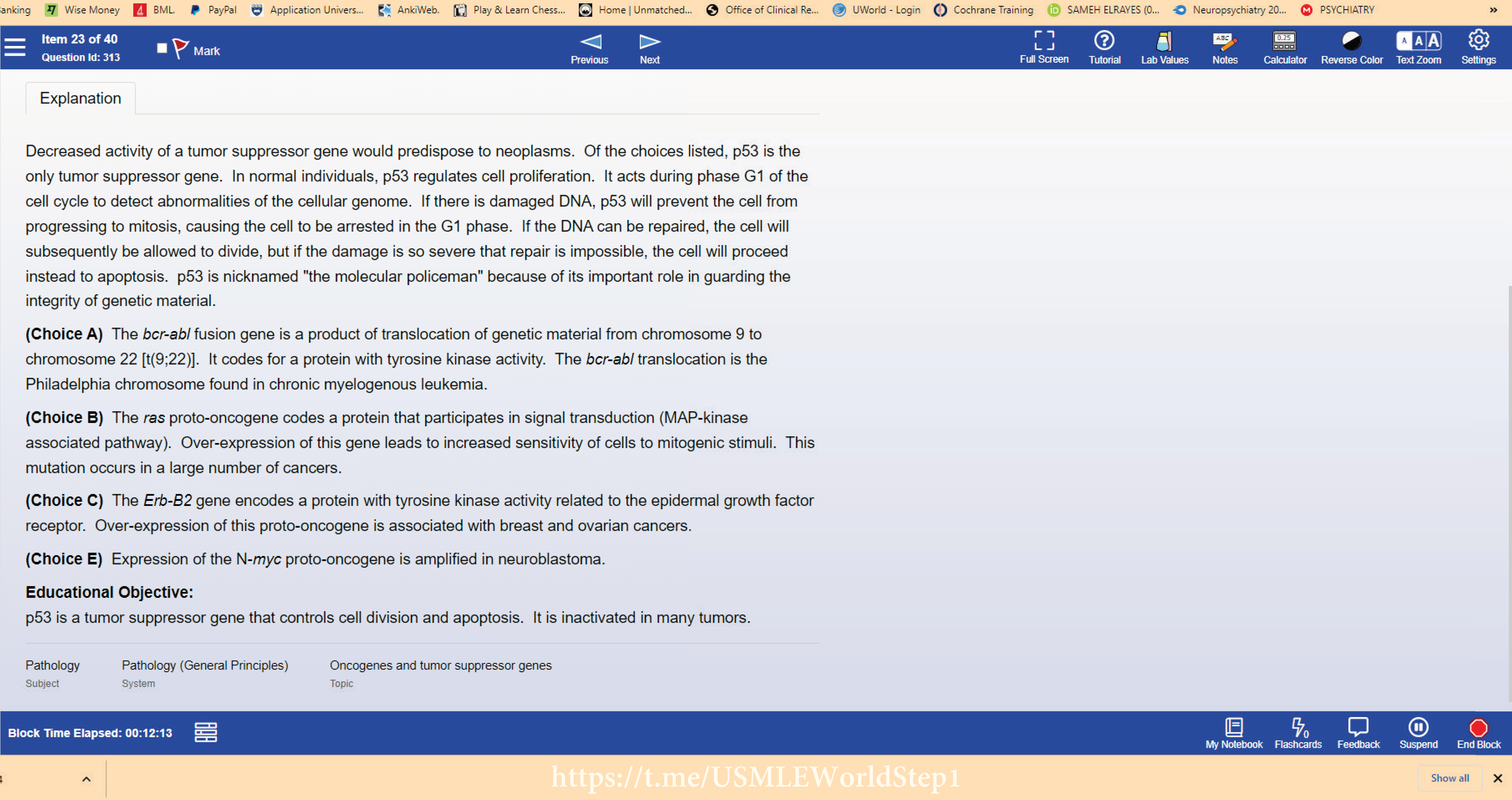
04 secs
Time Spent

2023
Version

Explanation

Decreased activity of a tumor suppressor gene would predispose to neoplasms. Of the choices listed, p53 is the only tumor suppressor gene. In normal individuals, p53 regulates cell proliferation. It acts during phase G1 of the cell cycle to detect abnormalities of the cellular genome. If there is damaged DNA, p53 will prevent the cell from progressing to mitosis, causing the cell to be arrested in the G1 phase. If the DNA can be repaired, the cell will subsequently be allowed to divide, but if the damage is so severe that repair is impossible, the cell will proceed instead to apoptosis. p53 is nicknamed "the molecular policeman" because of its important role in guarding the integrity of genetic material.

(Choice A) The *bcr-abl* fusion gene is a product of translocation of genetic material from chromosome 9 to chromosome 22 [t(9;22)]. It codes for a protein with tyrosine kinase activity. The *bcr-abl* translocation is the


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 23 of 40
Question Id: 313
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation

Decreased activity of a tumor suppressor gene would predispose to neoplasms. Of the choices listed, p53 is the only tumor suppressor gene. In normal individuals, p53 regulates cell proliferation. It acts during phase G1 of the cell cycle to detect abnormalities of the cellular genome. If there is damaged DNA, p53 will prevent the cell from progressing to mitosis, causing the cell to be arrested in the G1 phase. If the DNA can be repaired, the cell will subsequently be allowed to divide, but if the damage is so severe that repair is impossible, the cell will proceed instead to apoptosis. p53 is nicknamed "the molecular policeman" because of its important role in guarding the integrity of genetic material.

(Choice A) The *bcr-abl* fusion gene is a product of translocation of genetic material from chromosome 9 to chromosome 22 [t(9;22)]. It codes for a protein with tyrosine kinase activity. The *bcr-abl* translocation is the Philadelphia chromosome found in chronic myelogenous leukemia.

(Choice B) The *ras* proto-oncogene codes a protein that participates in signal transduction (MAP-kinase associated pathway). Over-expression of this gene leads to increased sensitivity of cells to mitogenic stimuli. This mutation occurs in a large number of cancers.

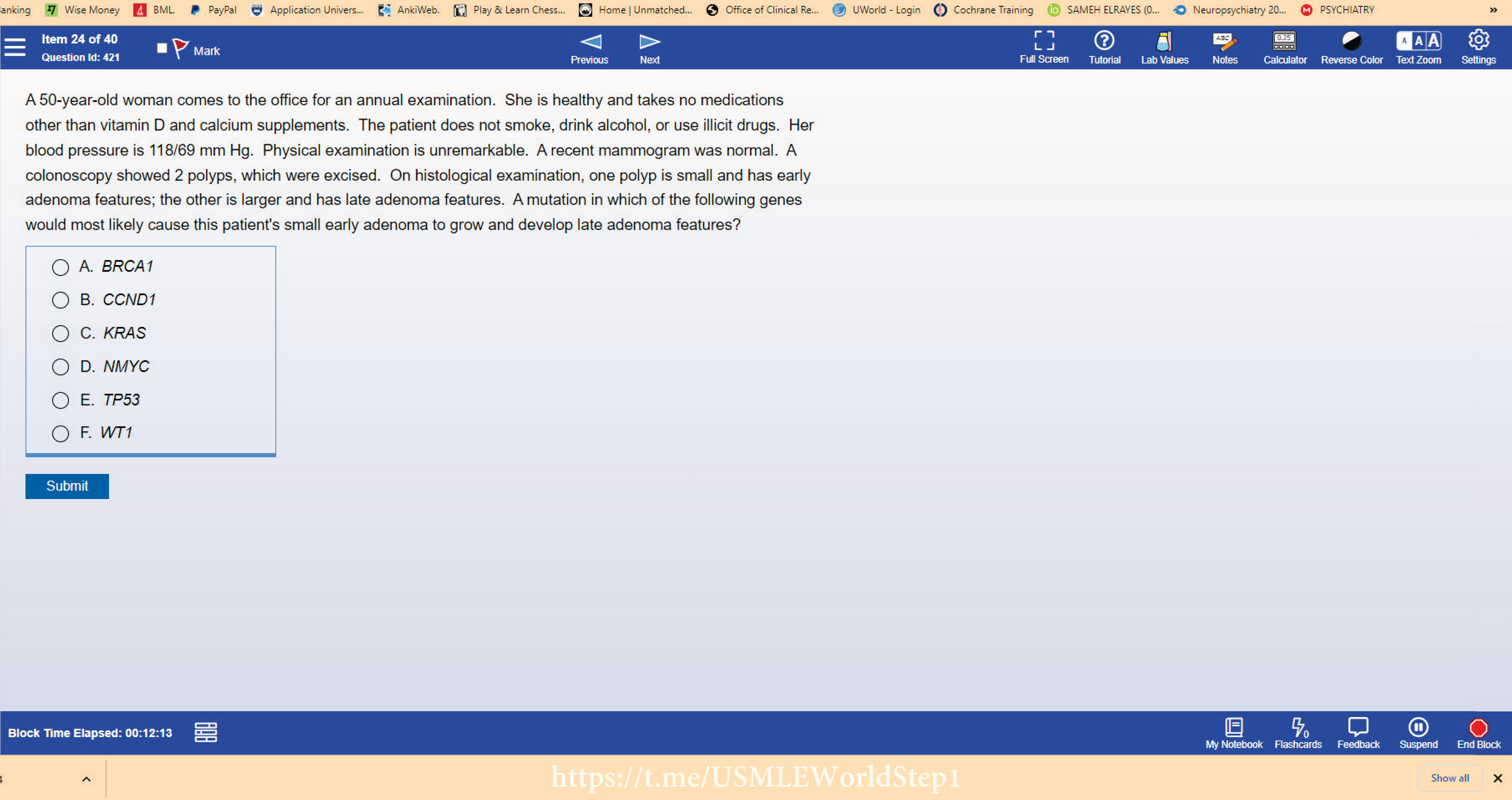
(Choice C) The *Erb-B2* gene encodes a protein with tyrosine kinase activity related to the epidermal growth factor receptor. Over-expression of this proto-oncogene is associated with breast and ovarian cancers.

(Choice E) Expression of the N-*myc* proto-oncogene is amplified in neuroblastoma.

Educational Objective:
p53 is a tumor suppressor gene that controls cell division and apoptosis. It is inactivated in many tumors.

Pathology	Pathology (General Principles)	Oncogenes and tumor suppressor genes
Subject	System	Topic

Block Time Elapsed: 00:12:13
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

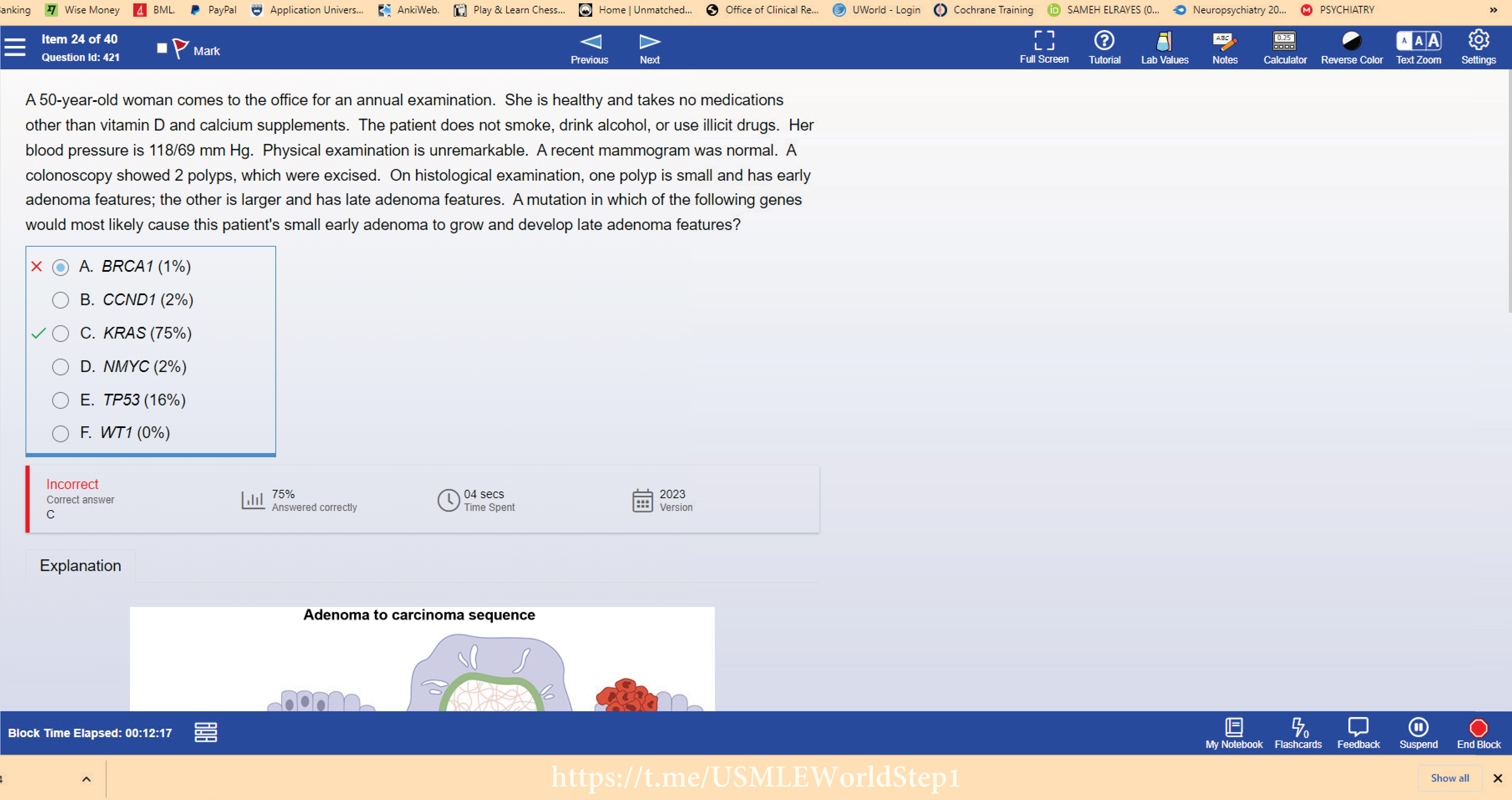

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 24 of 40
Question Id: 421
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 50-year-old woman comes to the office for an annual examination. She is healthy and takes no medications other than vitamin D and calcium supplements. The patient does not smoke, drink alcohol, or use illicit drugs. Her blood pressure is 118/69 mm Hg. Physical examination is unremarkable. A recent mammogram was normal. A colonoscopy showed 2 polyps, which were excised. On histological examination, one polyp is small and has early adenoma features; the other is larger and has late adenoma features. A mutation in which of the following genes would most likely cause this patient's small early adenoma to grow and develop late adenoma features?

○ A. *BRCA1*
○ B. *CCND1*
○ C. *KRAS*
○ D. *NMYC*
○ E. *TP53*
○ F. *WT1*

Block Time Elapsed: 00:12:13

My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Item 24 of 40
Question Id: 421
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:17
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 50-year-old woman comes to the office for an annual examination. She is healthy and takes no medications other than vitamin D and calcium supplements. The patient does not smoke, drink alcohol, or use illicit drugs. Her blood pressure is 118/69 mm Hg. Physical examination is unremarkable. A recent mammogram was normal. A colonoscopy showed 2 polyps, which were excised. On histological examination, one polyp is small and has early adenoma features; the other is larger and has late adenoma features. A mutation in which of the following genes would most likely cause this patient's small early adenoma to grow and develop late adenoma features?

- ✗ ● A. *BRCA1* (1%)
- ○ B. *CCND1* (2%)
- ✓ ○ C. *KRAS* (75%)
- ○ D. *NMYC* (2%)
- ○ E. *TP53* (16%)
- ○ F. *WT1* (0%)

Incorrect
Correct answer
C

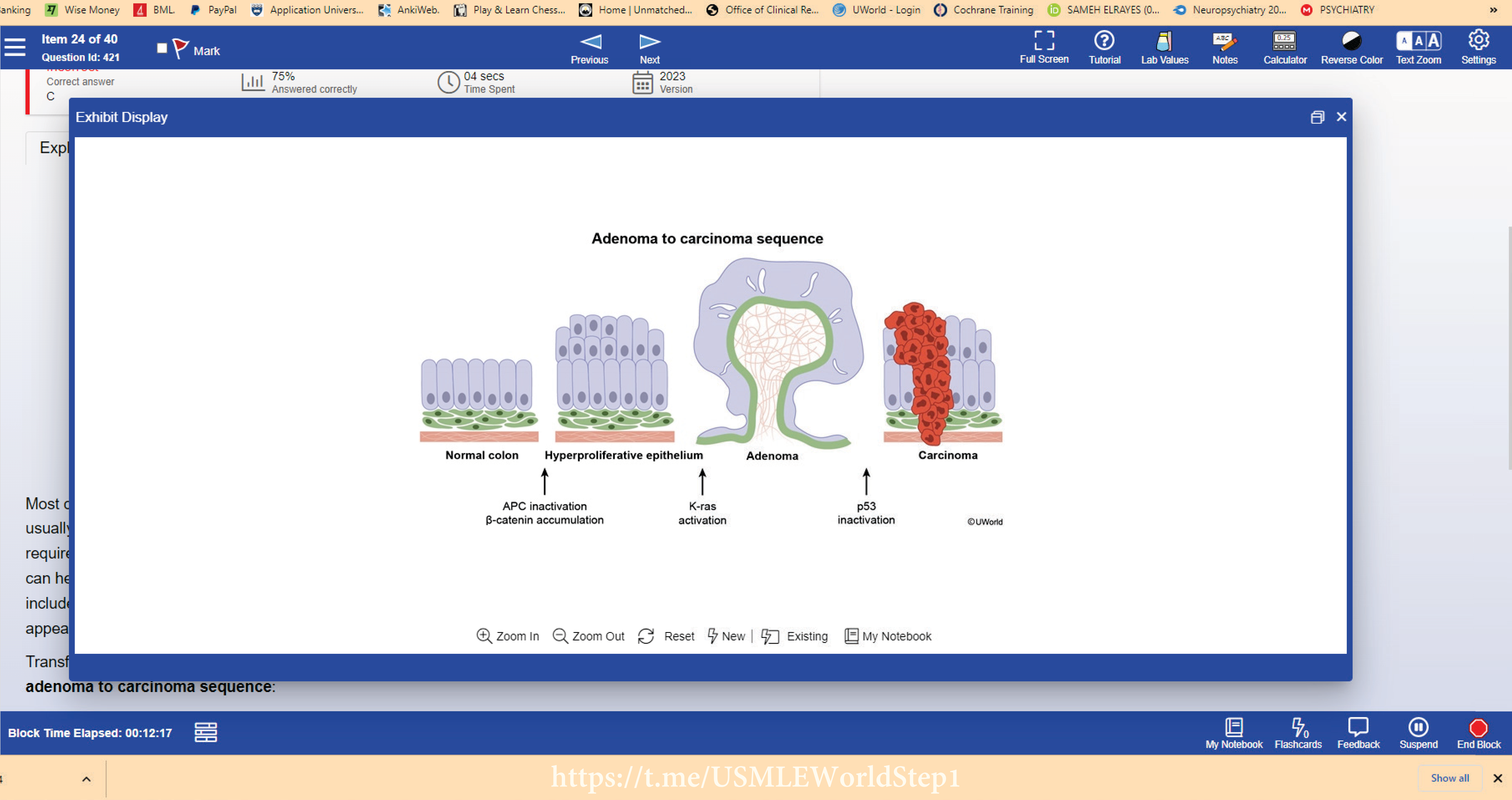
75%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

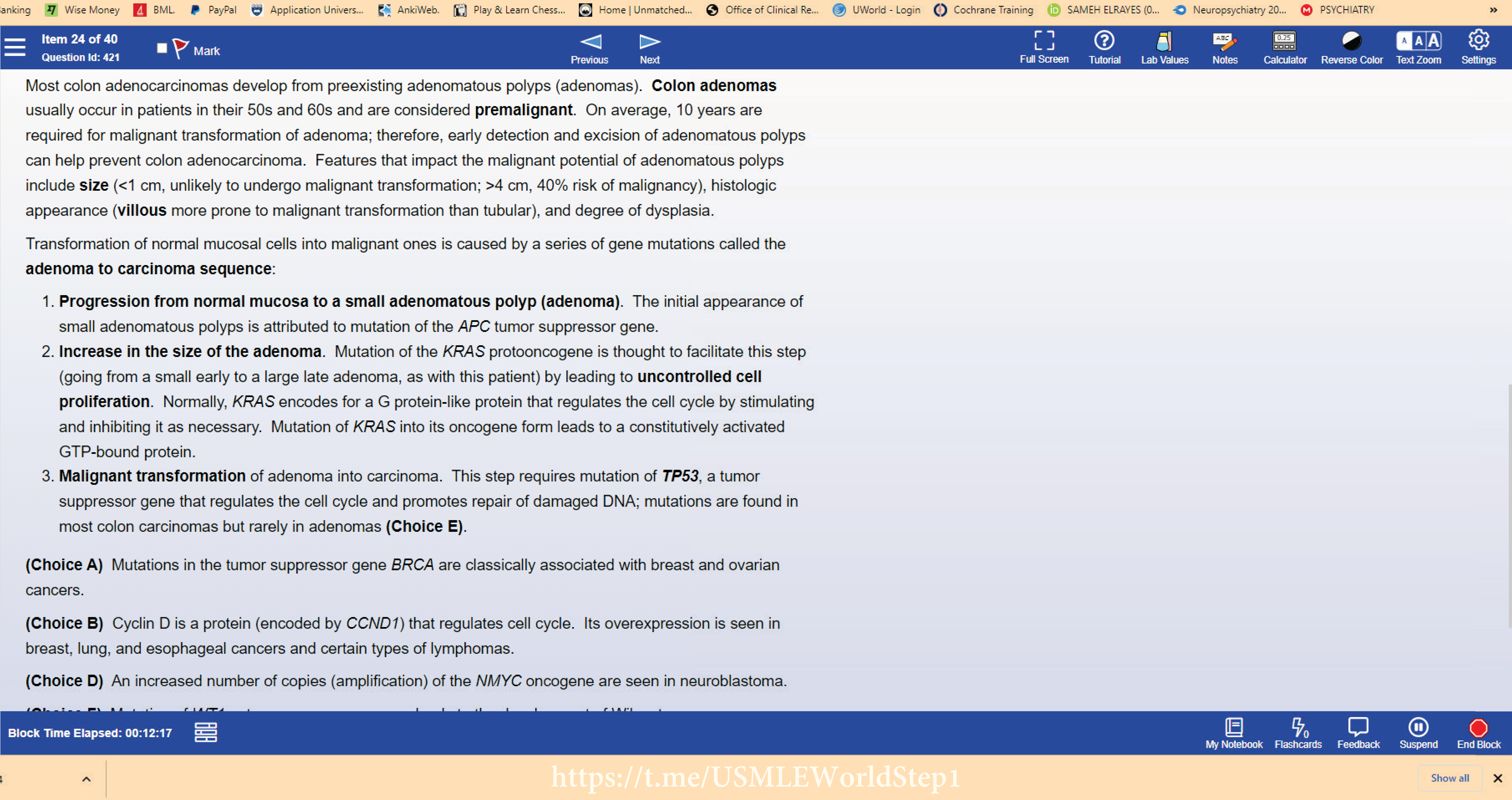
Adenoma to carcinoma sequence


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 24 of 40
Question Id: 421
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Correct answer
C
75%
Answered correctly
04 secs
Time Spent
2023
Version
Exhibit Display
Expl
Normal colon
Hyperproliferative epithelium
Adenoma
Carcinoma
APC inactivation
β-catenin accumulation
K-ras
activation
p53
inactivation
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:17
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Adenoma to carcinoma sequence

Most c
usually
require
can he
include
appea

Transf
adenoma to carcinoma sequence:


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 24 of 40
Question Id: 421
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:17
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Most colon adenocarcinomas develop from preexisting adenomatous polyps (adenomas). **Colon adenomas** usually occur in patients in their 50s and 60s and are considered **premalignant**. On average, 10 years are required for malignant transformation of adenoma; therefore, early detection and excision of adenomatous polyps can help prevent colon adenocarcinoma. Features that impact the malignant potential of adenomatous polyps include **size** (<1 cm, unlikely to undergo malignant transformation; >4 cm, 40% risk of malignancy), histologic appearance (**villous** more prone to malignant transformation than tubular), and degree of dysplasia.

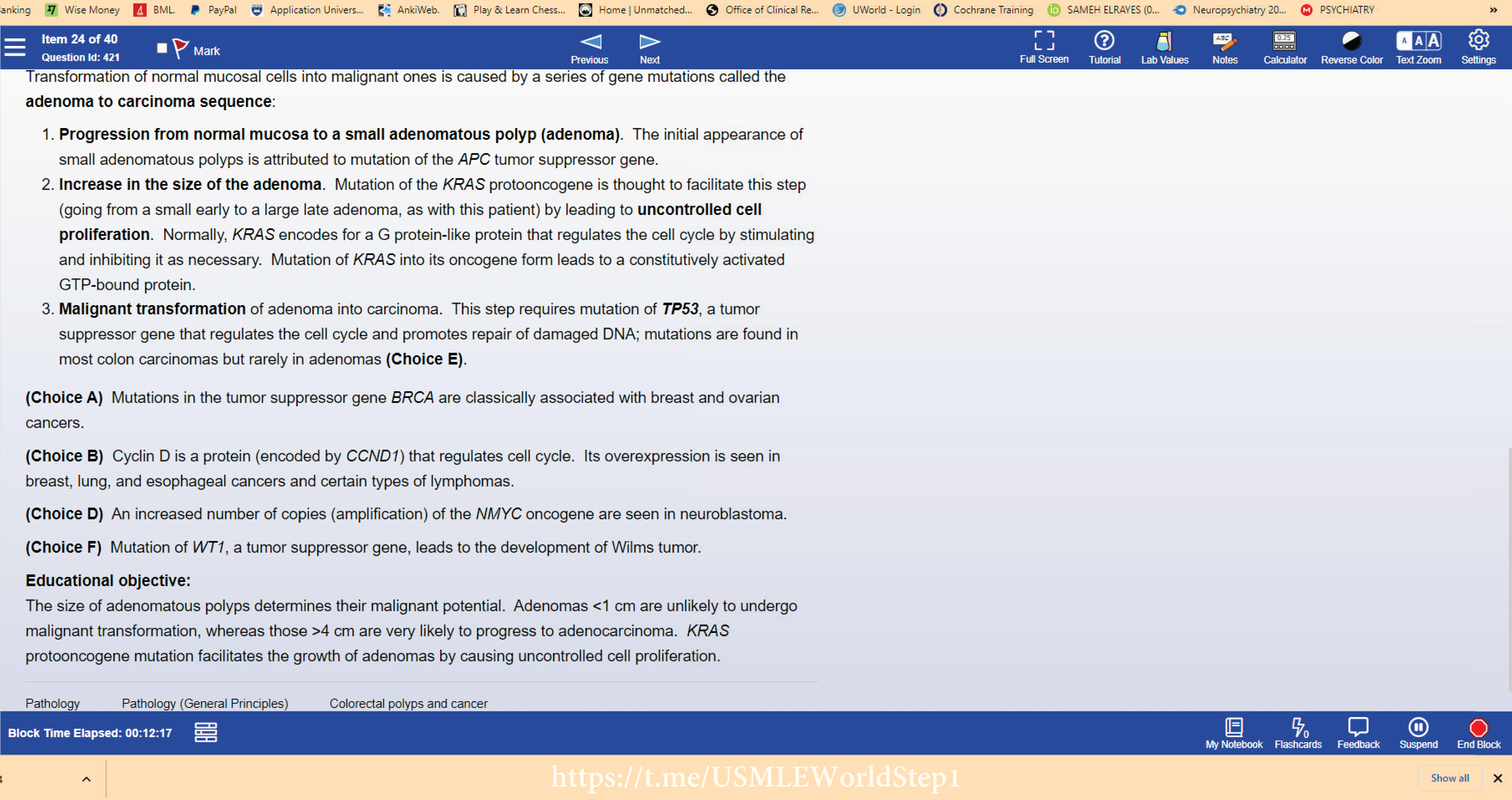
Transformation of normal mucosal cells into malignant ones is caused by a series of gene mutations called the **adenoma to carcinoma sequence**:

1. **Progression from normal mucosa to a small adenomatous polyp (adenoma)**. The initial appearance of small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene.
2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step (going from a small early to a large late adenoma, as with this patient) by leading to **uncontrolled cell proliferation**. Normally, *KRAS* encodes for a G protein-like protein that regulates the cell cycle by stimulating and inhibiting it as necessary. Mutation of *KRAS* into its oncogene form leads to a constitutively activated GTP-bound protein.
3. **Malignant transformation** of adenoma into carcinoma. This step requires mutation of ***TP53***, a tumor suppressor gene that regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely in adenomas **(Choice E)**.

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice D) An increased number of copies (amplification) of the *NMYC* oncogene are seen in neuroblastoma.


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 24 of 40
Question Id: 421
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:17
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Transformation of normal mucosal cells into malignant ones is caused by a series of gene mutations called the **adenoma to carcinoma sequence**:

1. **Progression from normal mucosa to a small adenomatous polyp (adenoma)**. The initial appearance of small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene.
2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step (going from a small early to a large late adenoma, as with this patient) by leading to **uncontrolled cell proliferation**. Normally, *KRAS* encodes for a G protein-like protein that regulates the cell cycle by stimulating and inhibiting it as necessary. Mutation of *KRAS* into its oncogene form leads to a constitutively activated GTP-bound protein.
3. **Malignant transformation** of adenoma into carcinoma. This step requires mutation of ***TP53***, a tumor suppressor gene that regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely in adenomas **(Choice E)**.

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice D) An increased number of copies (amplification) of the *NMYC* oncogene are seen in neuroblastoma.

(Choice F) Mutation of *WT1*, a tumor suppressor gene, leads to the development of Wilms tumor.

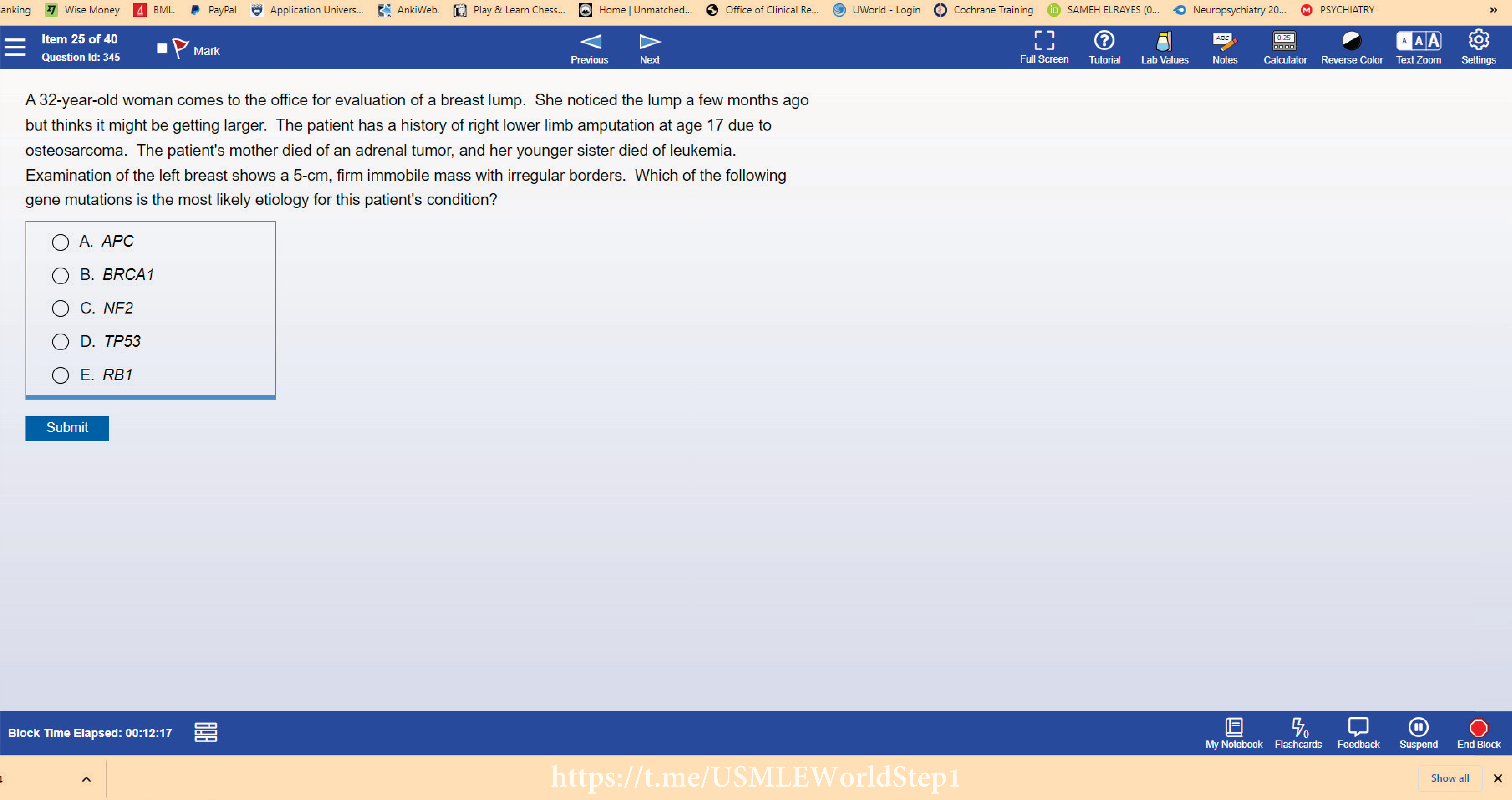
Educational objective:

The size of adenomatous polyps determines their malignant potential. Adenomas <1 cm are unlikely to undergo malignant transformation, whereas those >4 cm are very likely to progress to adenocarcinoma. *KRAS* protooncogene mutation facilitates the growth of adenomas by causing uncontrolled cell proliferation.

Pathology

Pathology (General Principles)

Colorectal polyps and cancer

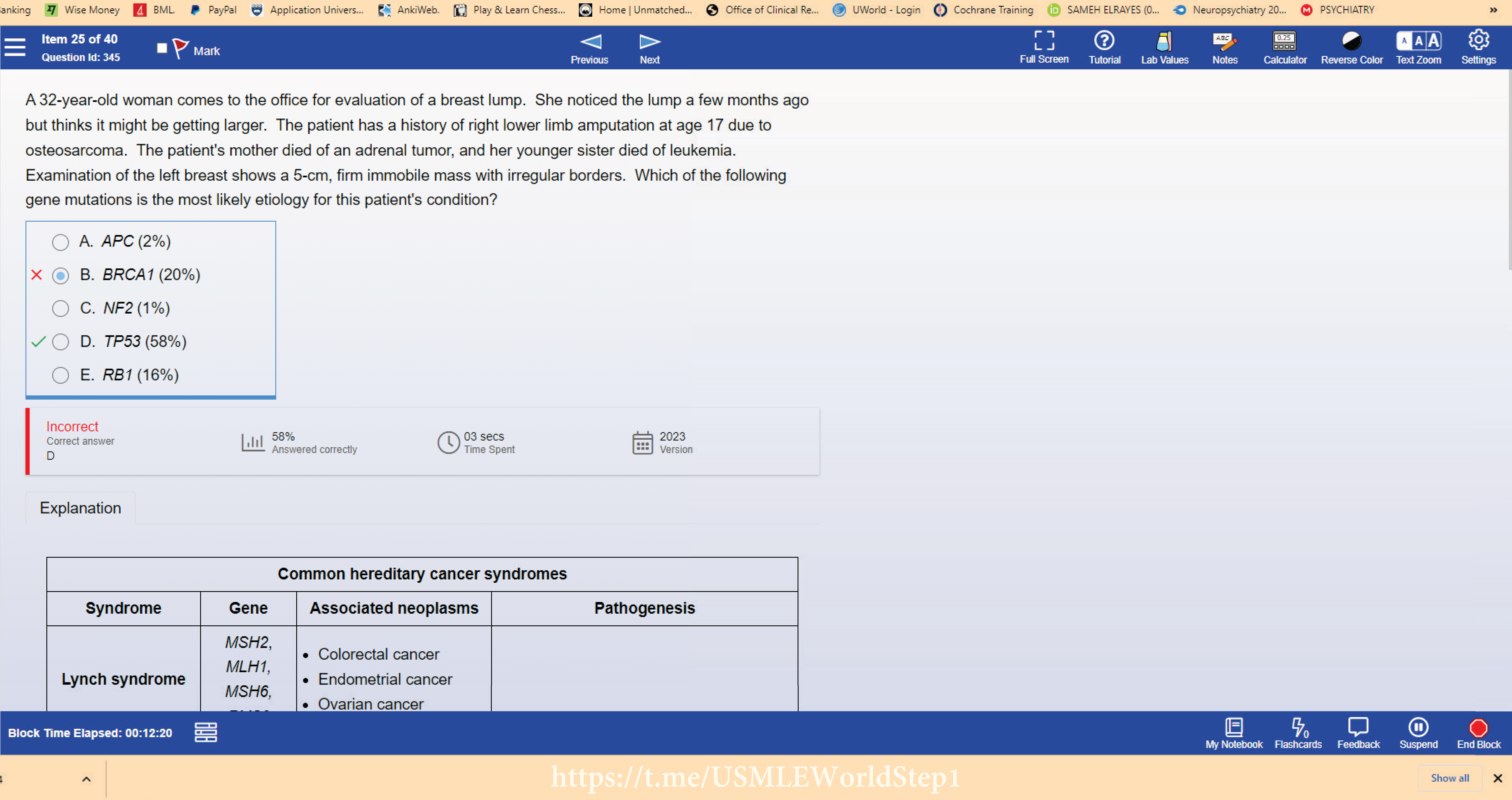

anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 25 of 40
Question Id: 345

A 32-year-old woman comes to the office for evaluation of a breast lump. She noticed the lump a few months ago but thinks it might be getting larger. The patient has a history of right lower limb amputation at age 17 due to osteosarcoma. The patient's mother died of an adrenal tumor, and her younger sister died of leukemia. Examination of the left breast shows a 5-cm, firm immobile mass with irregular borders. Which of the following gene mutations is the most likely etiology for this patient's condition?

○ A. *APC*
○ B. *BRCA1*
○ C. *NF2*
○ D. *TP53*
○ E. *RB1*

Block Time Elapsed: 00:12:17


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 32-year-old woman comes to the office for evaluation of a breast lump. She noticed the lump a few months ago but thinks it might be getting larger. The patient has a history of right lower limb amputation at age 17 due to osteosarcoma. The patient's mother died of an adrenal tumor, and her younger sister died of leukemia. Examination of the left breast shows a 5-cm, firm immobile mass with irregular borders. Which of the following gene mutations is the most likely etiology for this patient's condition?

- ○ A. *APC* (2%)
- ✗ ● B. *BRCA1* (20%)
- ○ C. *NF2* (1%)
- ✓ ○ D. *TP53* (58%)
- ○ E. *RB1* (16%)

Incorrect
Correct answer
D

58%
Answered correctly

03 secs
Time Spent

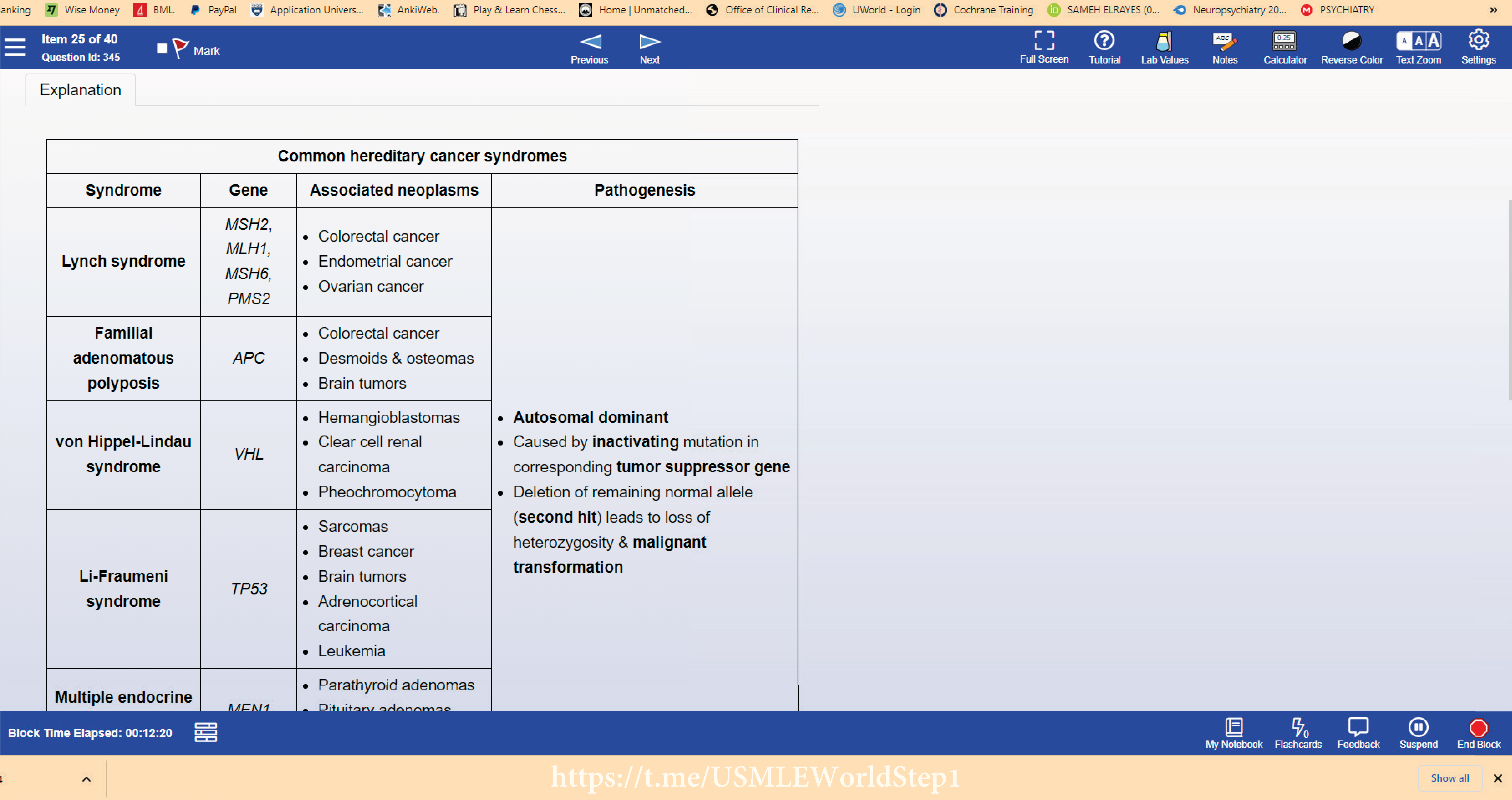
2023
Version

Explanation

Common hereditary cancer syndromes

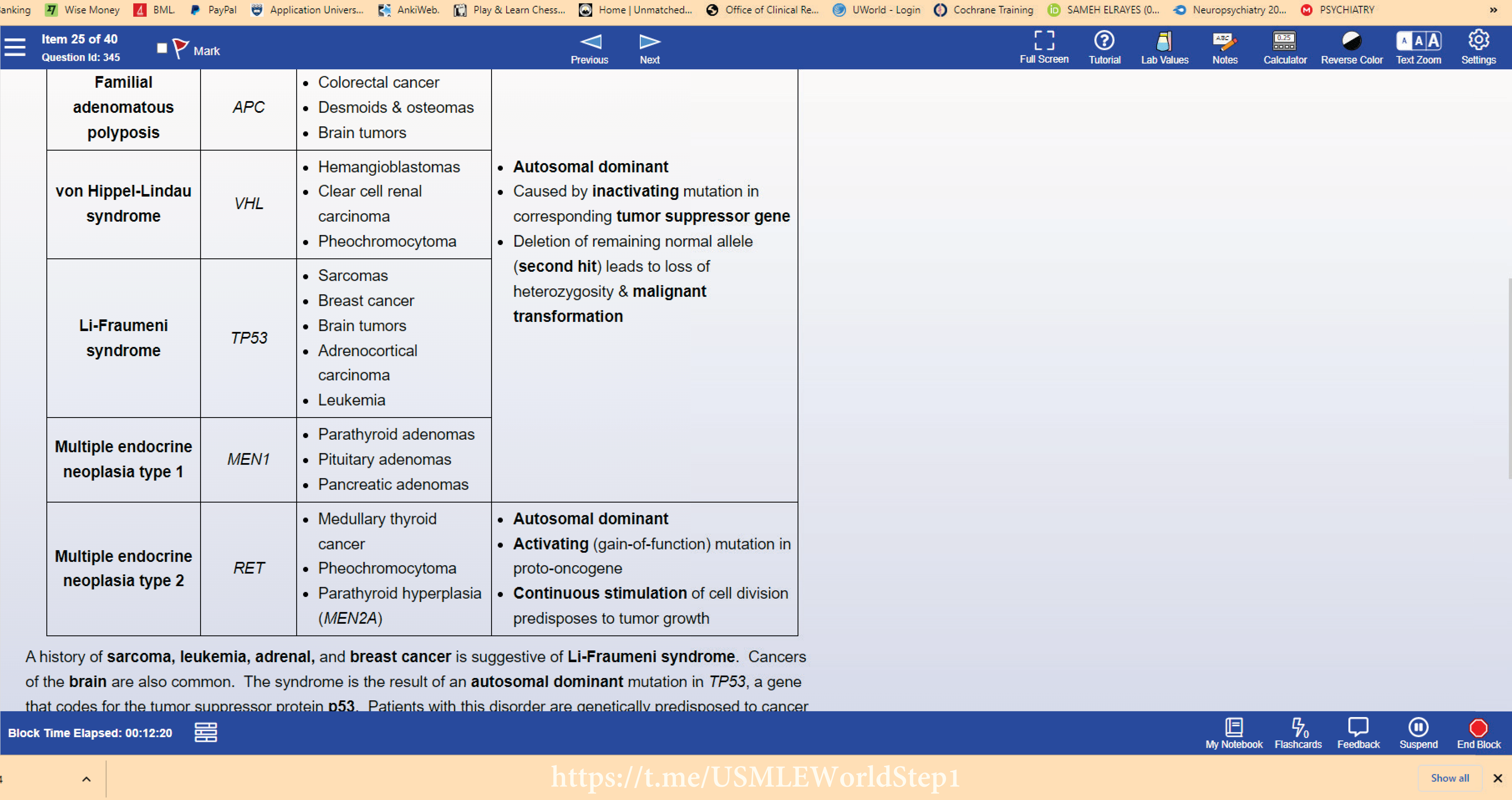
Syndrome	Gene	Associated neoplasms	Pathogenesis
Lynch syndrome	*MSH2,* *MLH1,* *MSH6,*	- Colorectal cancer - Endometrial cancer - Ovarian cancer	

https://t.me/USMLEWorldStep1


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Explanation
Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

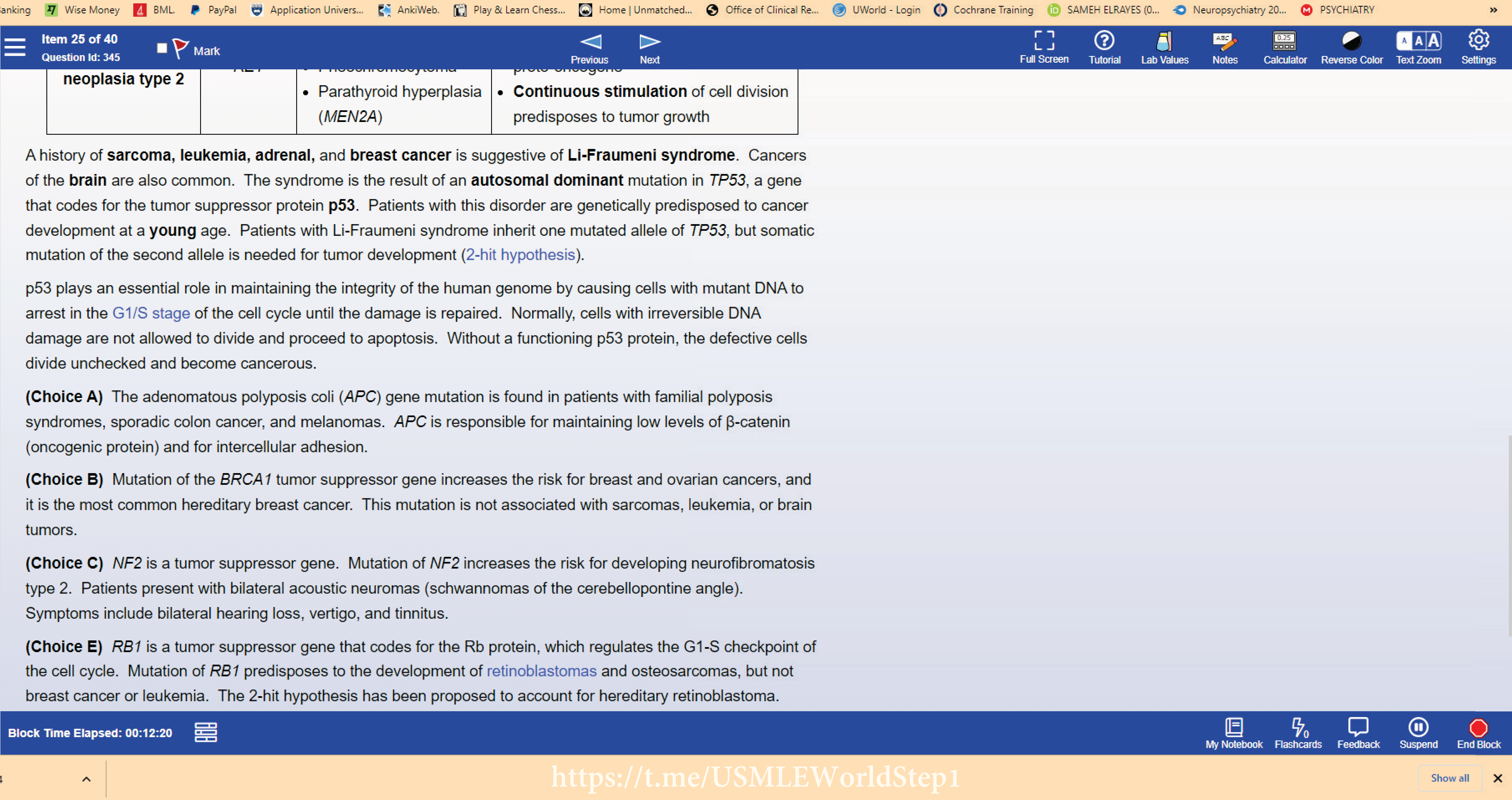
Common hereditary cancer syndromes

Syndrome	Gene	Associated neoplasms	Pathogenesis
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine	*MEN1*	• Parathyroid adenomas • Pituitary adenomas	


Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common. The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with this disorder are genetically predisposed to cancer


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

neoplasia type 2		- Parathyroid hyperplasia (*MEN2A*)	- **Continuous stimulation** of cell division predisposes to tumor growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common. The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with this disorder are genetically predisposed to cancer development at a **young** age. Patients with Li-Fraumeni syndrome inherit one mutated allele of *TP53*, but somatic mutation of the second allele is needed for tumor development (2-hit hypothesis).

p53 plays an essential role in maintaining the integrity of the human genome by causing cells with mutant DNA to arrest in the G1/S stage of the cell cycle until the damage is repaired. Normally, cells with irreversible DNA damage are not allowed to divide and proceed to apoptosis. Without a functioning p53 protein, the defective cells divide unchecked and become cancerous.

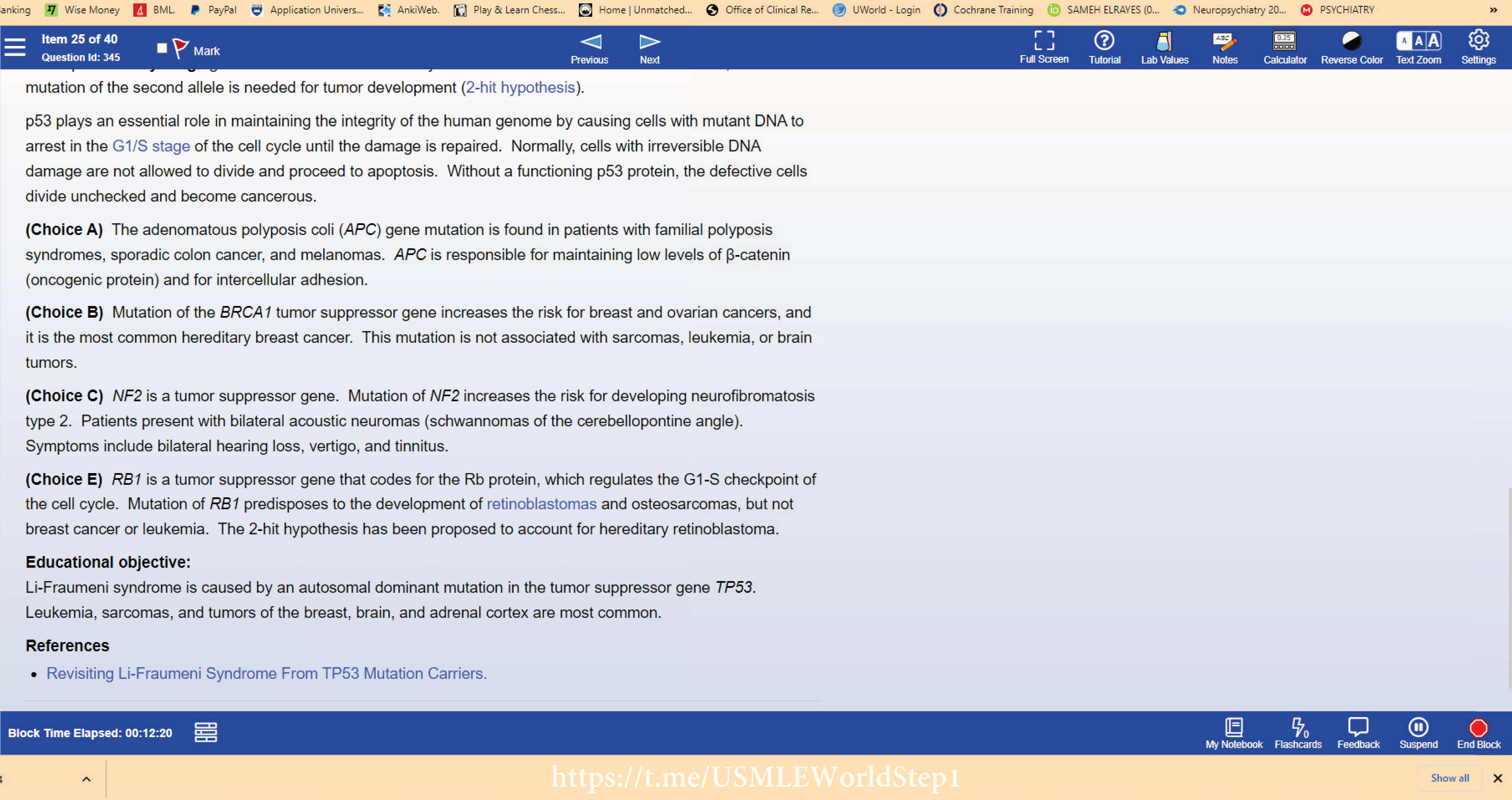
(Choice A) The adenomatous polyposis coli (*APC*) gene mutation is found in patients with familial polyposis syndromes, sporadic colon cancer, and melanomas. *APC* is responsible for maintaining low levels of β-catenin (oncogenic protein) and for intercellular adhesion.

(Choice B) Mutation of the *BRCA1* tumor suppressor gene increases the risk for breast and ovarian cancers, and it is the most common hereditary breast cancer. This mutation is not associated with sarcomas, leukemia, or brain tumors.

(Choice C) *NF2* is a tumor suppressor gene. Mutation of *NF2* increases the risk for developing neurofibromatosis type 2. Patients present with bilateral acoustic neuromas (schwannomas of the cerebellopontine angle). Symptoms include bilateral hearing loss, vertigo, and tinnitus.

(Choice E) *RB1* is a tumor suppressor gene that codes for the Rb protein, which regulates the G1-S checkpoint of the cell cycle. Mutation of *RB1* predisposes to the development of retinoblastomas and osteosarcomas, but not breast cancer or leukemia. The 2-hit hypothesis has been proposed to account for hereditary retinoblastoma.

Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

mutation of the second allele is needed for tumor development (2-hit hypothesis).

p53 plays an essential role in maintaining the integrity of the human genome by causing cells with mutant DNA to arrest in the G1/S stage of the cell cycle until the damage is repaired. Normally, cells with irreversible DNA damage are not allowed to divide and proceed to apoptosis. Without a functioning p53 protein, the defective cells divide unchecked and become cancerous.

(Choice A) The adenomatous polyposis coli (*APC*) gene mutation is found in patients with familial polyposis syndromes, sporadic colon cancer, and melanomas. *APC* is responsible for maintaining low levels of β-catenin (oncogenic protein) and for intercellular adhesion.

(Choice B) Mutation of the *BRCA1* tumor suppressor gene increases the risk for breast and ovarian cancers, and it is the most common hereditary breast cancer. This mutation is not associated with sarcomas, leukemia, or brain tumors.

(Choice C) *NF2* is a tumor suppressor gene. Mutation of *NF2* increases the risk for developing neurofibromatosis type 2. Patients present with bilateral acoustic neuromas (schwannomas of the cerebellopontine angle). Symptoms include bilateral hearing loss, vertigo, and tinnitus.

(Choice E) *RB1* is a tumor suppressor gene that codes for the Rb protein, which regulates the G1-S checkpoint of the cell cycle. Mutation of *RB1* predisposes to the development of retinoblastomas and osteosarcomas, but not breast cancer or leukemia. The 2-hit hypothesis has been proposed to account for hereditary retinoblastoma.

Educational objective:

Li-Fraumeni syndrome is caused by an autosomal dominant mutation in the tumor suppressor gene *TP53*. Leukemia, sarcomas, and tumors of the breast, brain, and adrenal cortex are most common.

References

- Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers.

Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 25 of 40
Question Id: 345

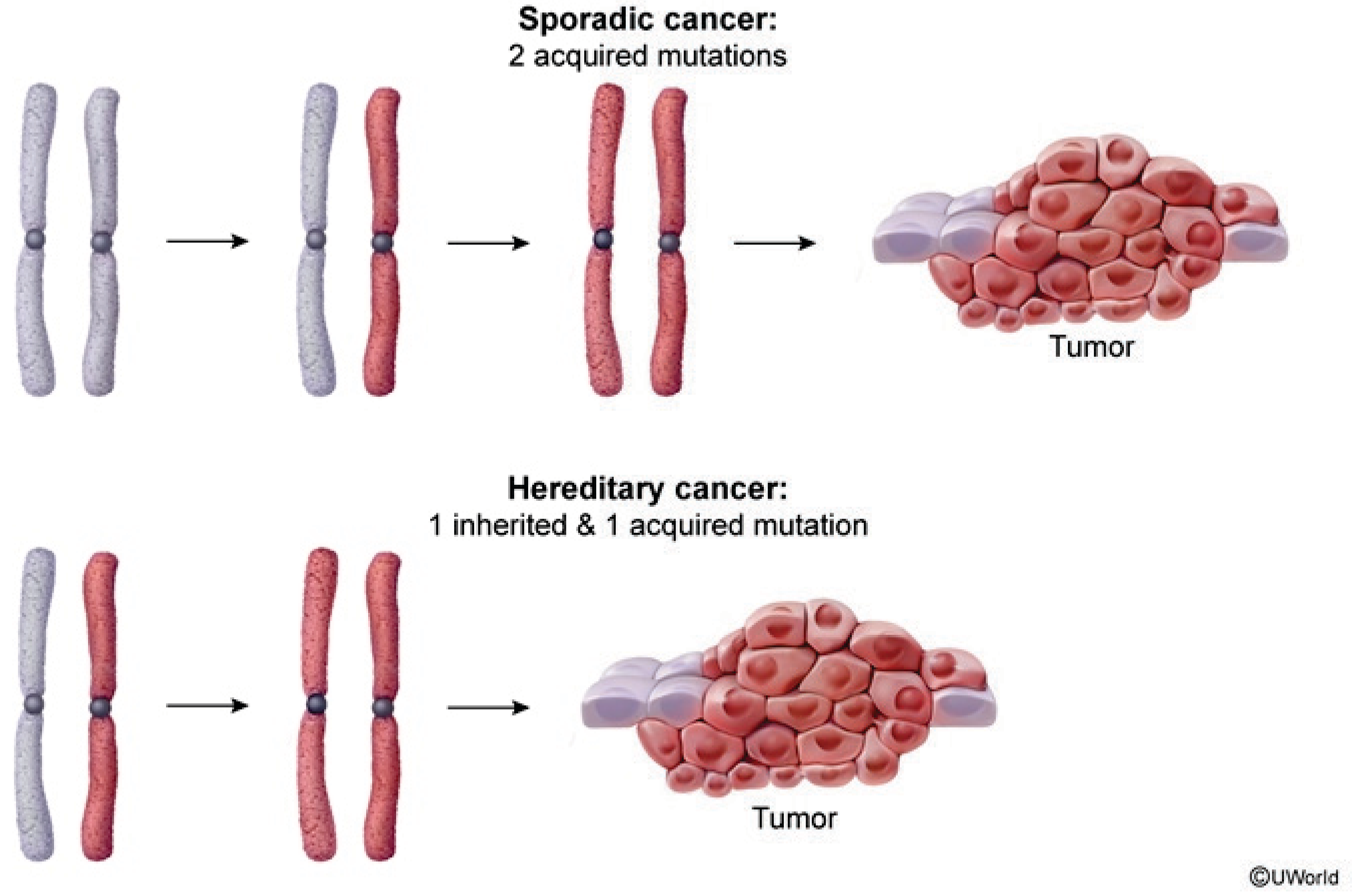
☐ Mark

Previous | Next | Full Screen | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom | Settings

Exhibit Display

Knudson's 2-hit hypothesis

Both copies of the gene must be knocked out to promote malignancy.



Sporadic cancer:
2 acquired mutations
Tumor
Hereditary cancer:
1 inherited & 1 acquired mutation
Tumor

©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

A histo
of the
that co
develo
mutati

p53 pl
arrest
damag
divide

(Choi
syndro
(oncog

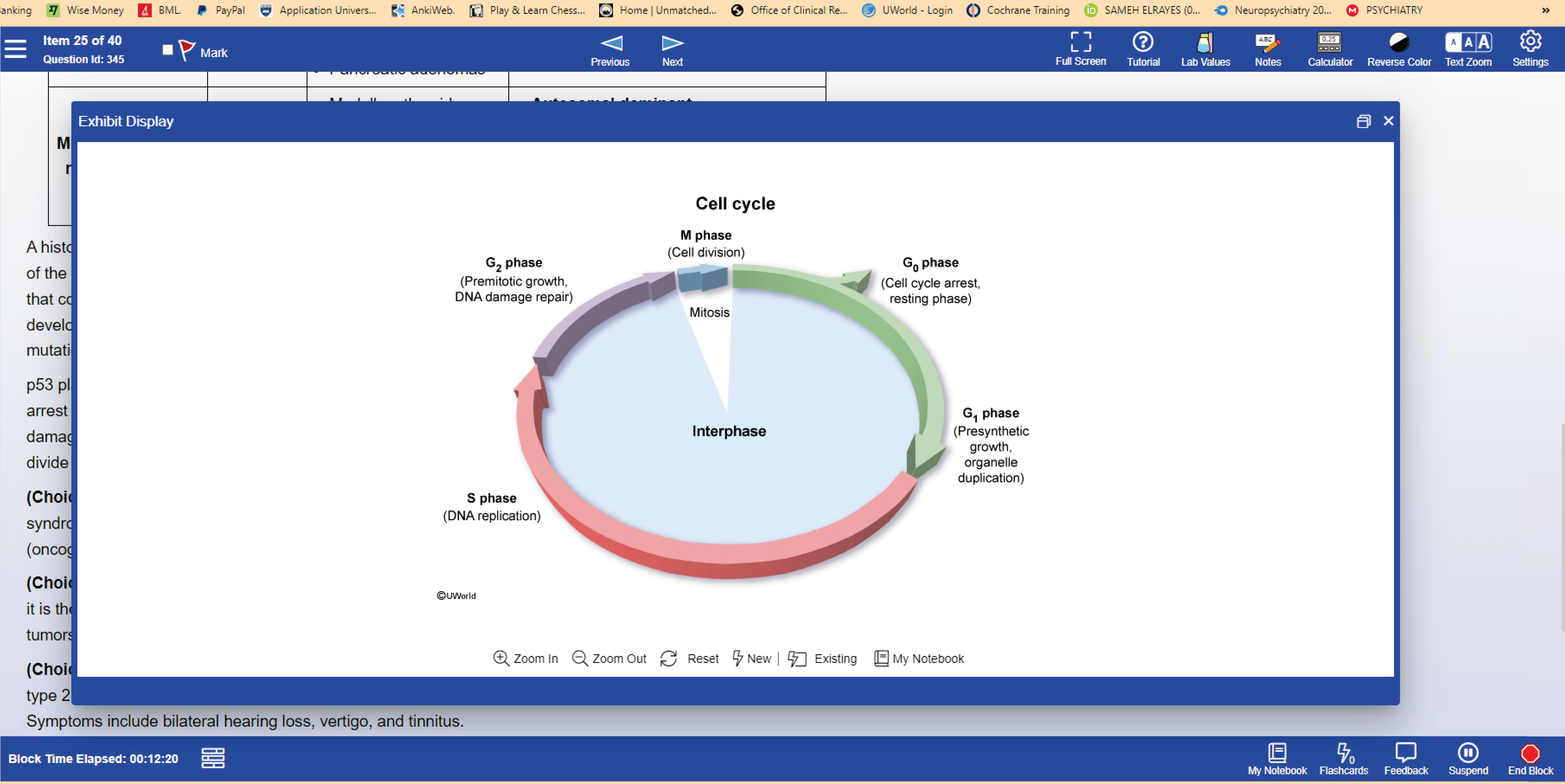
(Choi
it is the
tumors

(Choi
type 2

Symptoms include bilateral hearing loss, vertigo, and tinnitus.

Block Time Elapsed: 00:12:20

My Notebook | Flashcards | Feedback | Suspend | End Block


Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Cell cycle
M phase
(Cell division)
G$_2$ phase
(Premitotic growth,
DNA damage repair)
G$_0$ phase
(Cell cycle arrest,
resting phase)
Mitosis
Interphase
G$_1$ phase
(Presynthetic
growth,
organelle
duplication)
S phase
(DNA replication)
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block

A histo
of the
that co
develo
mutati

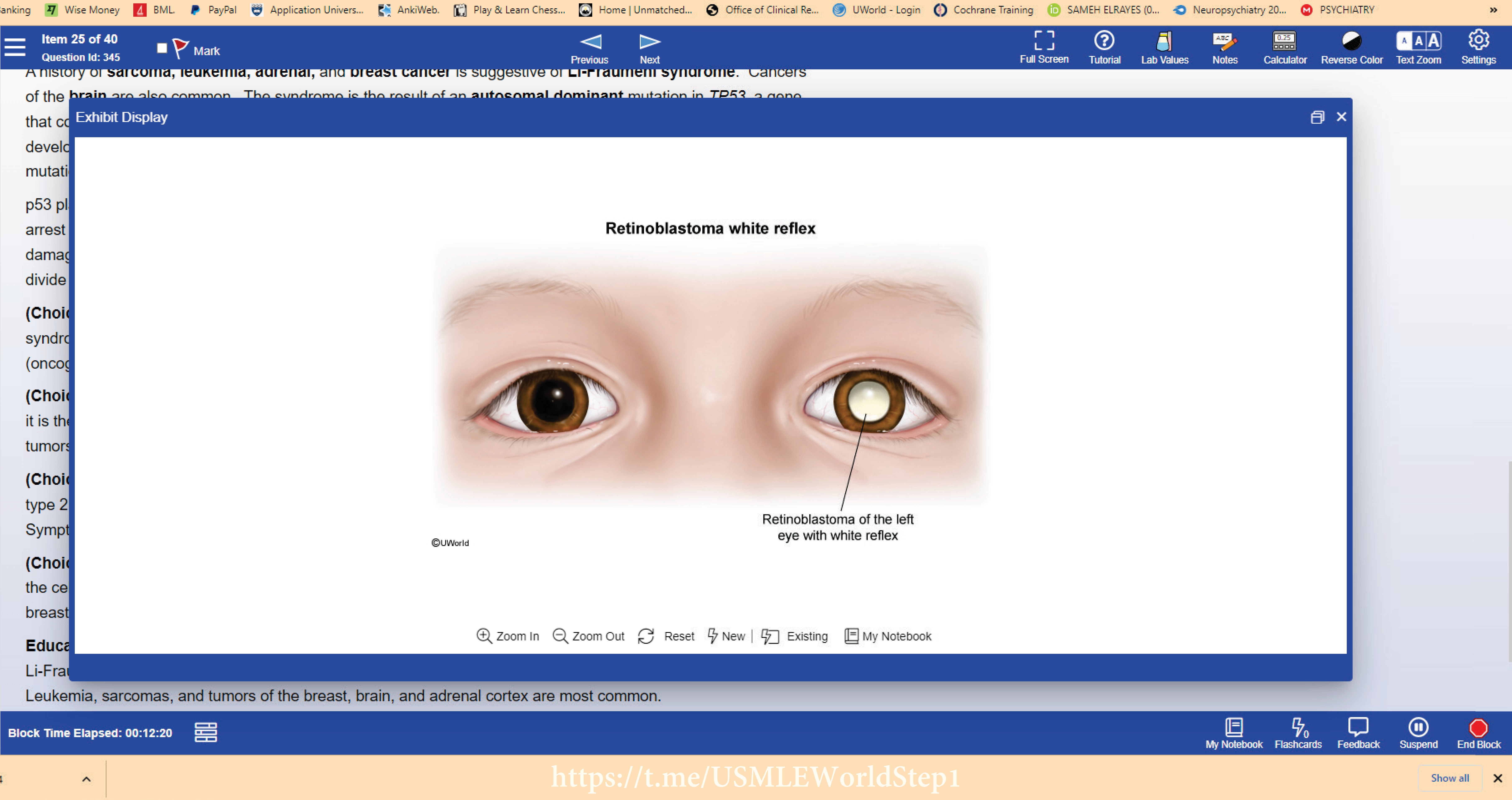
p53 pl
arrest
damag
divide

(Choi
syndro
(oncog

(Choi
it is the
tumors

(Choi
type 2

Symptoms include bilateral hearing loss, vertigo, and tinnitus.


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 25 of 40
Question Id: 345
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common. The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene

that co

develo

mutati

p53 pl

arrest

damag

divide

(Choi

syndro

(oncog

(Choi

it is the

tumors

(Choi

type 2

Sympt

(Choi

the ce

breast

Educa

Li-Frau

Leukemia, sarcomas, and tumors of the breast, brain, and adrenal cortex are most common.

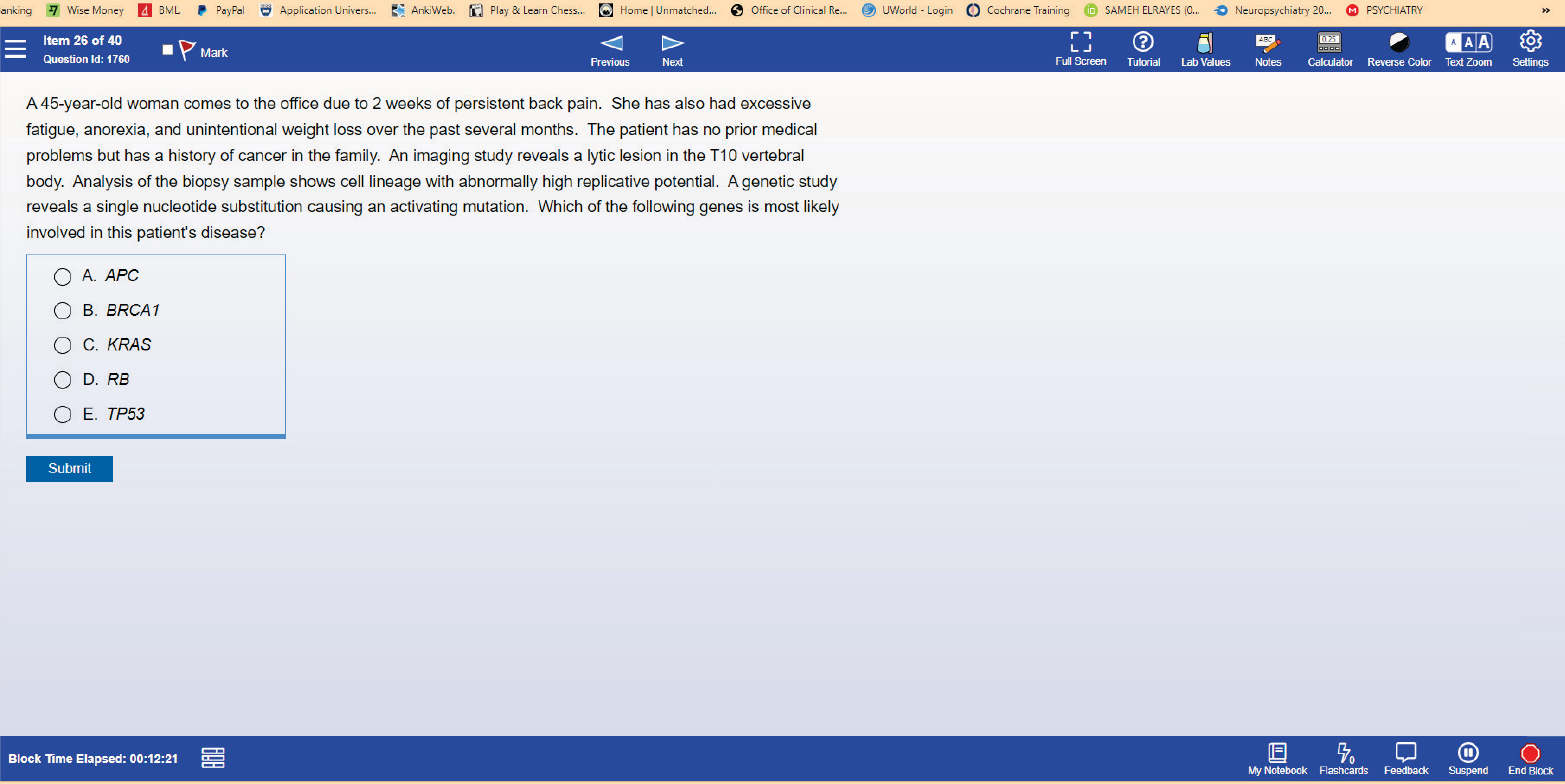
Exhibit Display

Retinoblastoma white reflex

Retinoblastoma of the left eye with white reflex

©UWorld

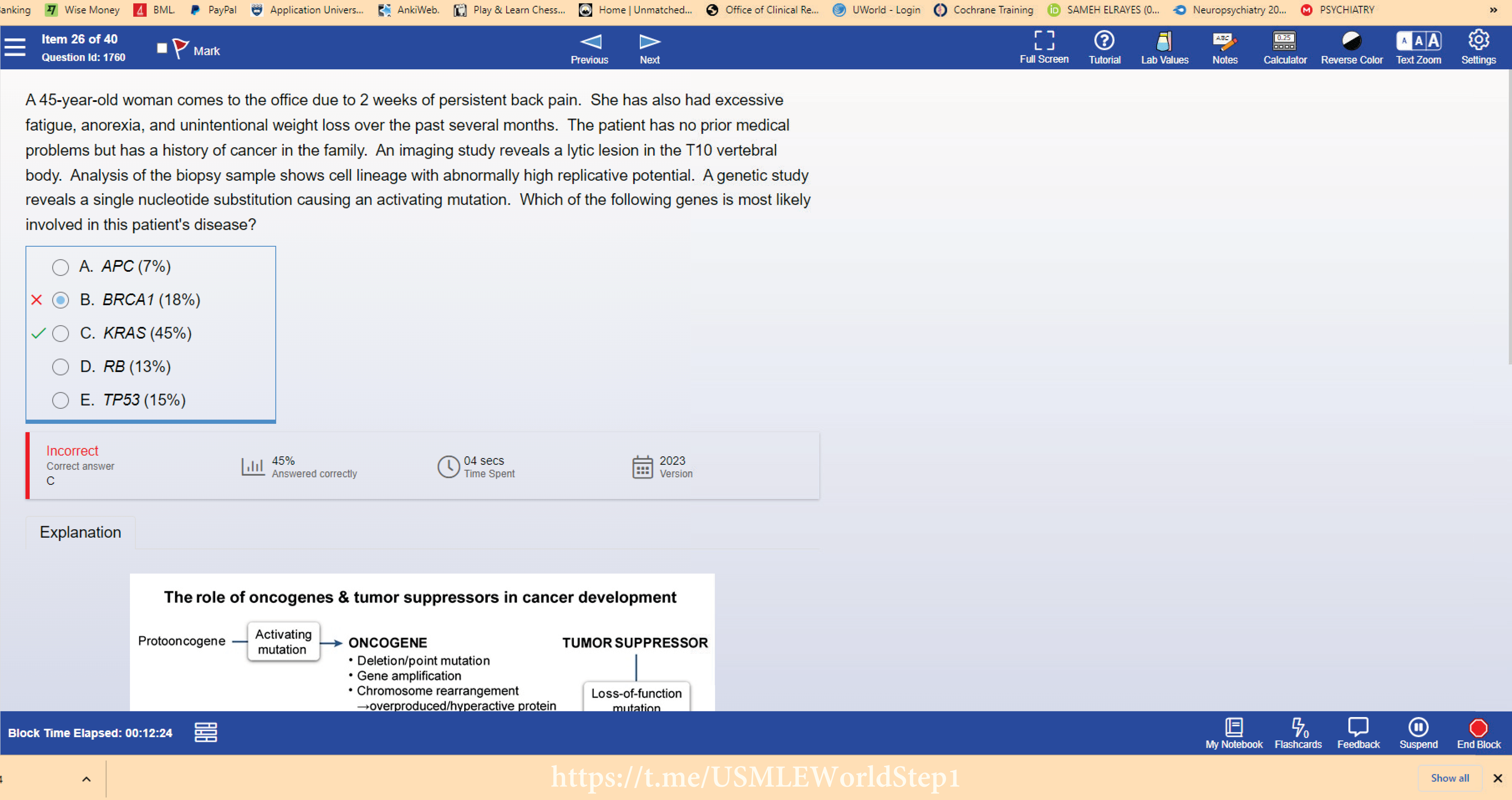
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:20
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 26 of 40
Question Id: 1760
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 45-year-old woman comes to the office due to 2 weeks of persistent back pain. She has also had excessive fatigue, anorexia, and unintentional weight loss over the past several months. The patient has no prior medical problems but has a history of cancer in the family. An imaging study reveals a lytic lesion in the T10 vertebral body. Analysis of the biopsy sample shows cell lineage with abnormally high replicative potential. A genetic study reveals a single nucleotide substitution causing an activating mutation. Which of the following genes is most likely involved in this patient's disease?

○ A. *APC*
○ B. *BRCA1*
○ C. *KRAS*
○ D. *RB*
○ E. *TP53*

Submit
Block Time Elapsed: 00:12:21
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 26 of 40
Question Id: 1760
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 45-year-old woman comes to the office due to 2 weeks of persistent back pain. She has also had excessive fatigue, anorexia, and unintentional weight loss over the past several months. The patient has no prior medical problems but has a history of cancer in the family. An imaging study reveals a lytic lesion in the T10 vertebral body. Analysis of the biopsy sample shows cell lineage with abnormally high replicative potential. A genetic study reveals a single nucleotide substitution causing an activating mutation. Which of the following genes is most likely involved in this patient's disease?

- ○ A. *APC* (7%)
- ✗ ● B. *BRCA1* (18%)
- ✓ ○ C. *KRAS* (45%)
- ○ D. *RB* (13%)
- ○ E. *TP53* (15%)

Incorrect
Correct answer
C

45%
Answered correctly

04 secs
Time Spent

2023
Version

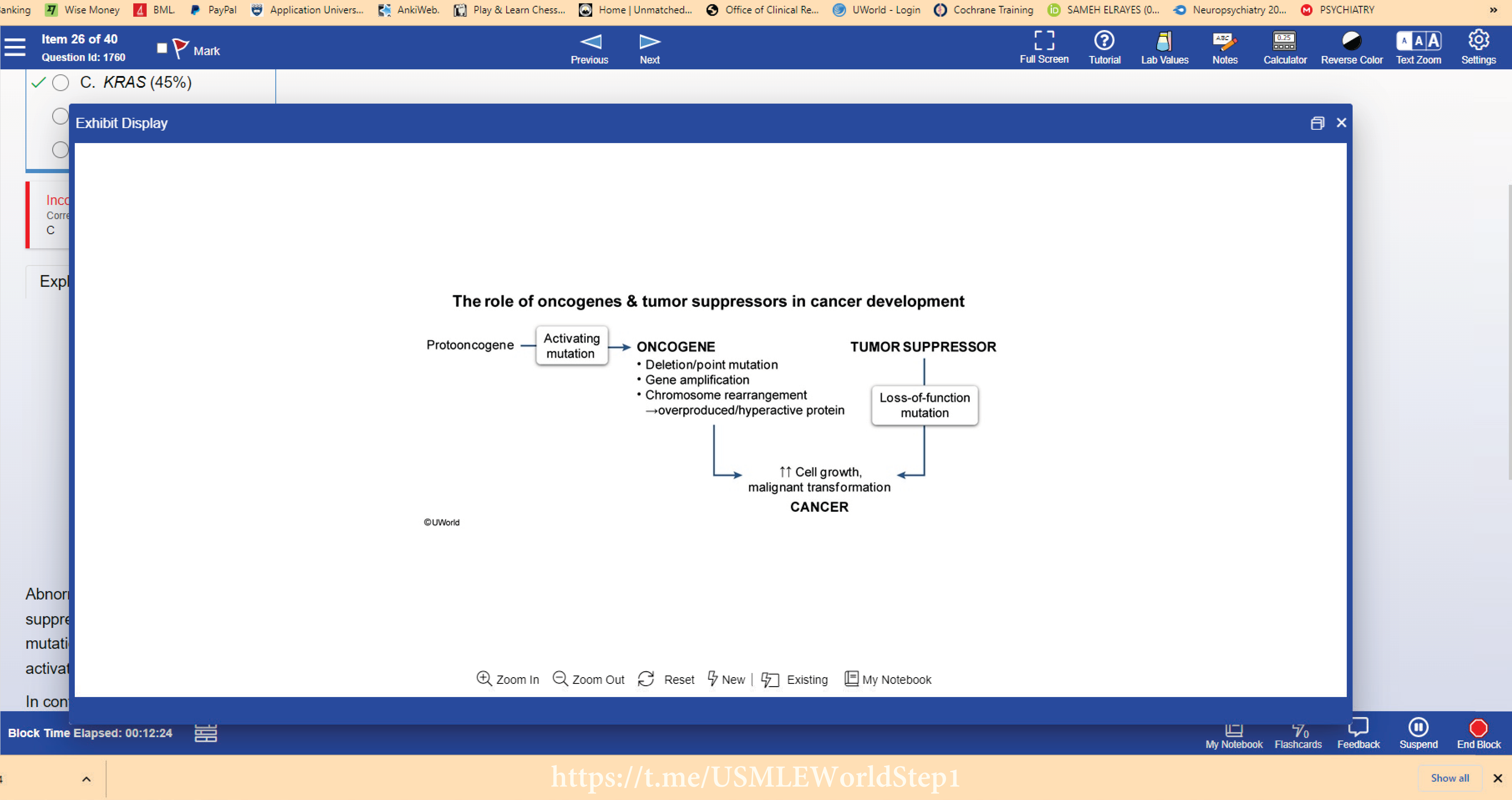
Explanation

The role of oncogenes & tumor suppressors in cancer development

Protooncogene
Activating mutation
ONCOGENE
TUMOR SUPPRESSOR
Loss-of-function mutation

ONCOGENE
- Deletion/point mutation
- Gene amplification
- Chromosome rearrangement →overproduced/hyperactive protein

Block Time Elapsed: 00:12:24
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 26 of 40
Question Id: 1760
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

✓ ○ C. *KRAS* (45%)

○

○

Inco
Corre
C
Expl
Abnor
suppre
mutati
activat
In con

Exhibit Display

The role of oncogenes & tumor suppressors in cancer development

Protooncogene → Activating mutation → **ONCOGENE**

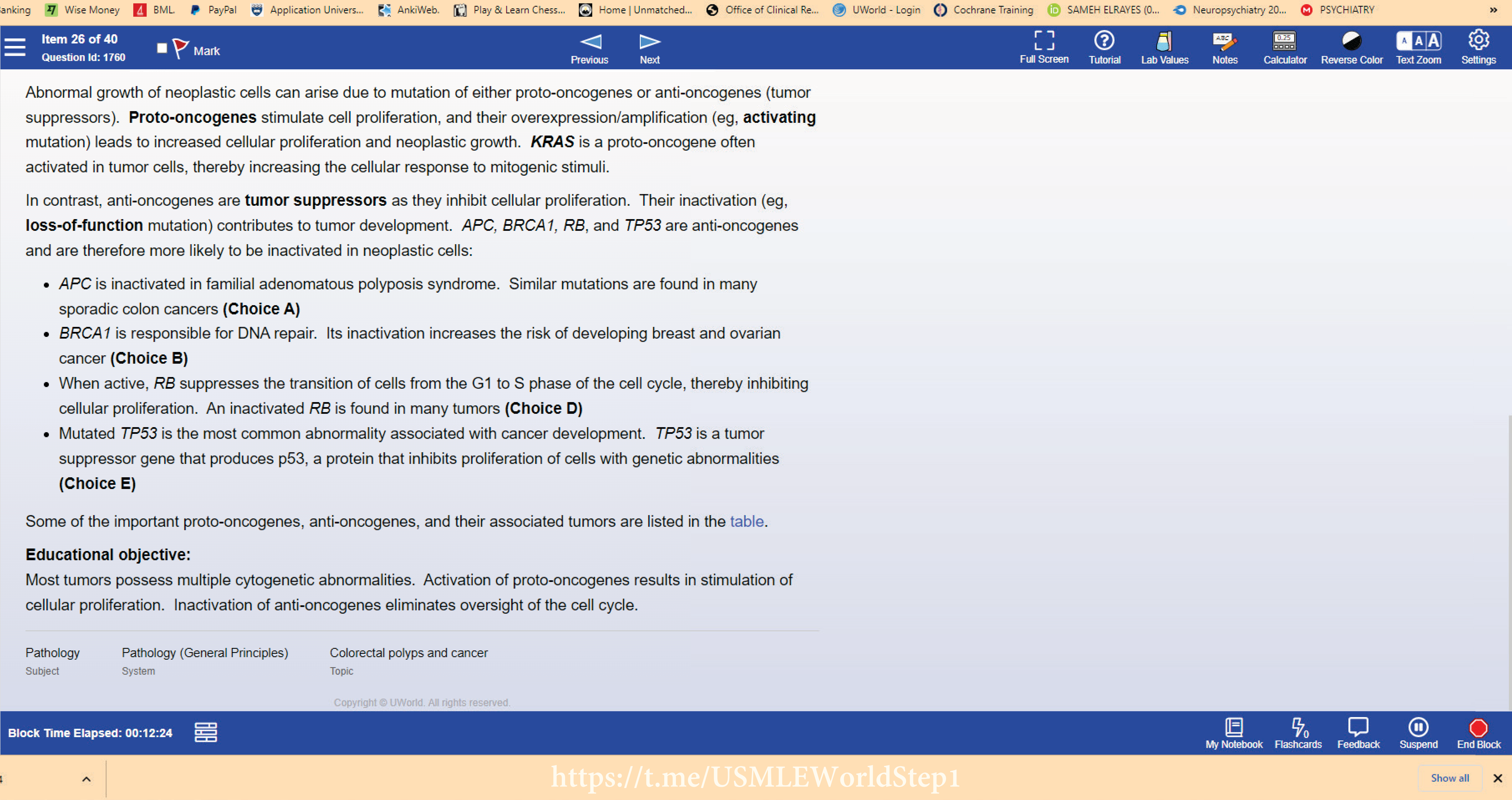
- Deletion/point mutation
- Gene amplification
- Chromosome rearrangement
  →overproduced/hyperactive protein

TUMOR SUPPRESSOR → Loss-of-function mutation

↑↑ Cell growth,
malignant transformation
CANCER

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:24
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Item 26 of 40
Question Id: 1760
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Abnormal growth of neoplastic cells can arise due to mutation of either proto-oncogenes or anti-oncogenes (tumor suppressors). **Proto-oncogenes** stimulate cell proliferation, and their overexpression/amplification (eg, **activating** mutation) leads to increased cellular proliferation and neoplastic growth. ***KRAS*** is a proto-oncogene often activated in tumor cells, thereby increasing the cellular response to mitogenic stimuli.

In contrast, anti-oncogenes are **tumor suppressors** as they inhibit cellular proliferation. Their inactivation (eg, **loss-of-function** mutation) contributes to tumor development. *APC, BRCA1, RB*, and *TP53* are anti-oncogenes and are therefore more likely to be inactivated in neoplastic cells:

- *APC* is inactivated in familial adenomatous polyposis syndrome. Similar mutations are found in many sporadic colon cancers **(Choice A)**
- *BRCA1* is responsible for DNA repair. Its inactivation increases the risk of developing breast and ovarian cancer **(Choice B)**
- When active, *RB* suppresses the transition of cells from the G1 to S phase of the cell cycle, thereby inhibiting cellular proliferation. An inactivated *RB* is found in many tumors **(Choice D)**
- Mutated *TP53* is the most common abnormality associated with cancer development. *TP53* is a tumor suppressor gene that produces p53, a protein that inhibits proliferation of cells with genetic abnormalities **(Choice E)**

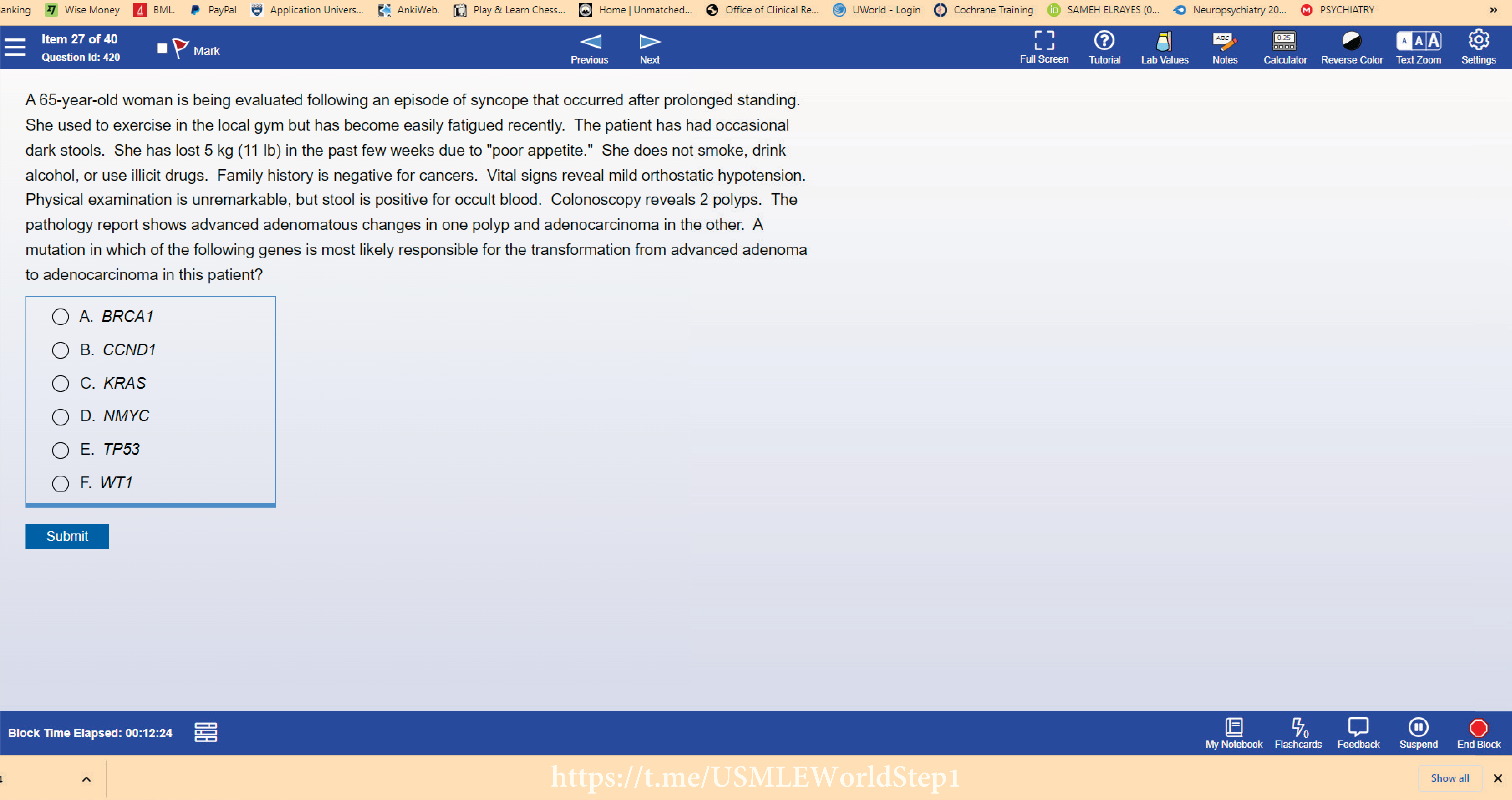
Some of the important proto-oncogenes, anti-oncogenes, and their associated tumors are listed in the table.

Educational objective:
Most tumors possess multiple cytogenetic abnormalities. Activation of proto-oncogenes results in stimulation of cellular proliferation. Inactivation of anti-oncogenes eliminates oversight of the cell cycle.

Pathology	Pathology (General Principles)	Colorectal polyps and cancer
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Block Time Elapsed: 00:12:24
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

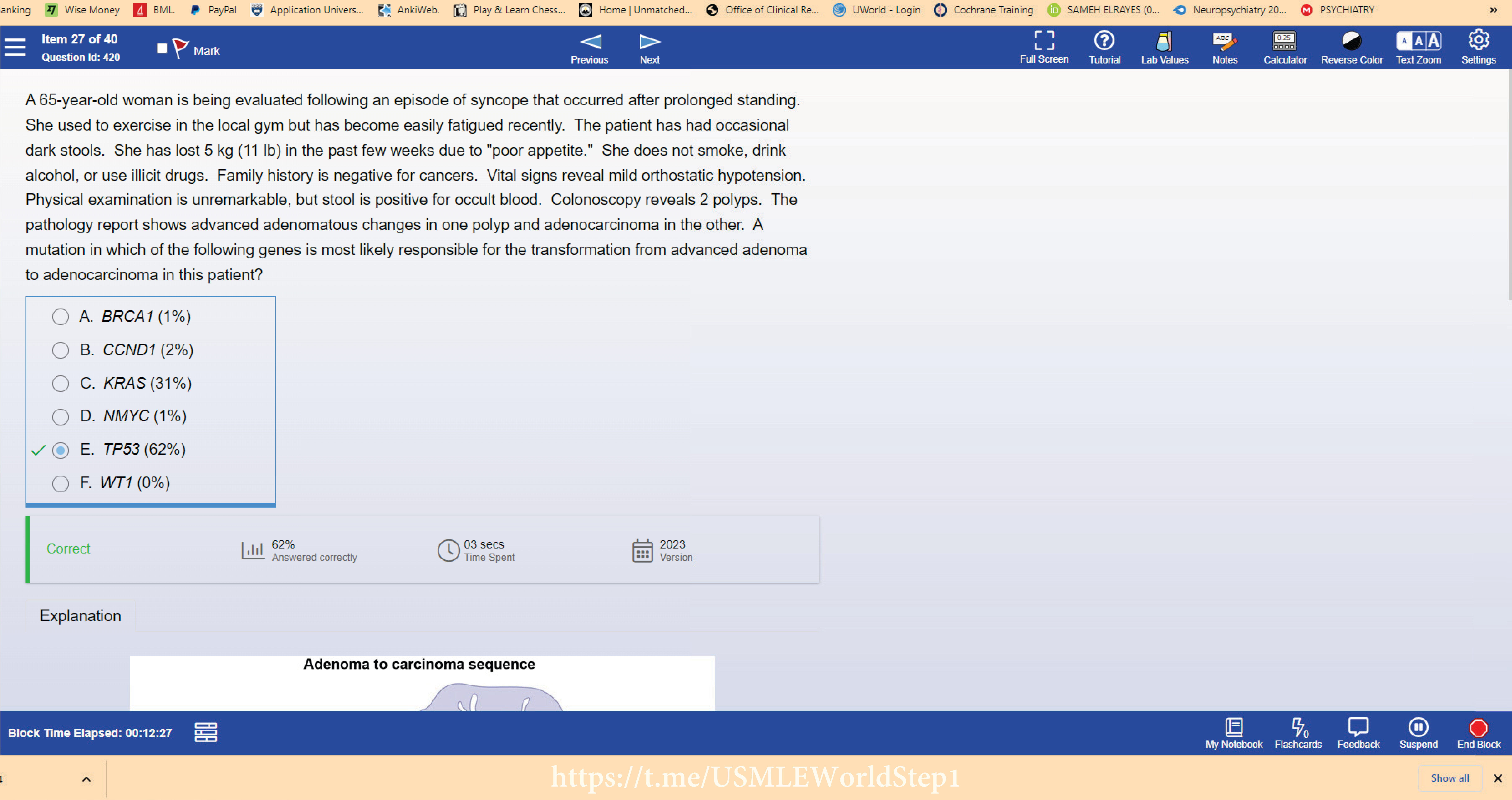
Item 27 of 40
Question Id: 420

A 65-year-old woman is being evaluated following an episode of syncope that occurred after prolonged standing. She used to exercise in the local gym but has become easily fatigued recently. The patient has had occasional dark stools. She has lost 5 kg (11 lb) in the past few weeks due to "poor appetite." She does not smoke, drink alcohol, or use illicit drugs. Family history is negative for cancers. Vital signs reveal mild orthostatic hypotension. Physical examination is unremarkable, but stool is positive for occult blood. Colonoscopy reveals 2 polyps. The pathology report shows advanced adenomatous changes in one polyp and adenocarcinoma in the other. A mutation in which of the following genes is most likely responsible for the transformation from advanced adenoma to adenocarcinoma in this patient?

○ A. *BRCA1*
○ B. *CCND1*
○ C. *KRAS*
○ D. *NMYC*
○ E. *TP53*
○ F. *WT1*

Submit

Block Time Elapsed: 00:12:24


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 27 of 40
Question Id: 420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 65-year-old woman is being evaluated following an episode of syncope that occurred after prolonged standing. She used to exercise in the local gym but has become easily fatigued recently. The patient has had occasional dark stools. She has lost 5 kg (11 lb) in the past few weeks due to "poor appetite." She does not smoke, drink alcohol, or use illicit drugs. Family history is negative for cancers. Vital signs reveal mild orthostatic hypotension. Physical examination is unremarkable, but stool is positive for occult blood. Colonoscopy reveals 2 polyps. The pathology report shows advanced adenomatous changes in one polyp and adenocarcinoma in the other. A mutation in which of the following genes is most likely responsible for the transformation from advanced adenoma to adenocarcinoma in this patient?

- ○ A. *BRCA1* (1%)
- ○ B. *CCND1* (2%)
- ○ C. *KRAS* (31%)
- ○ D. *NMYC* (1%)
- ✓ ● E. *TP53* (62%)
- ○ F. *WT1* (0%)

Correct

62% Answered correctly

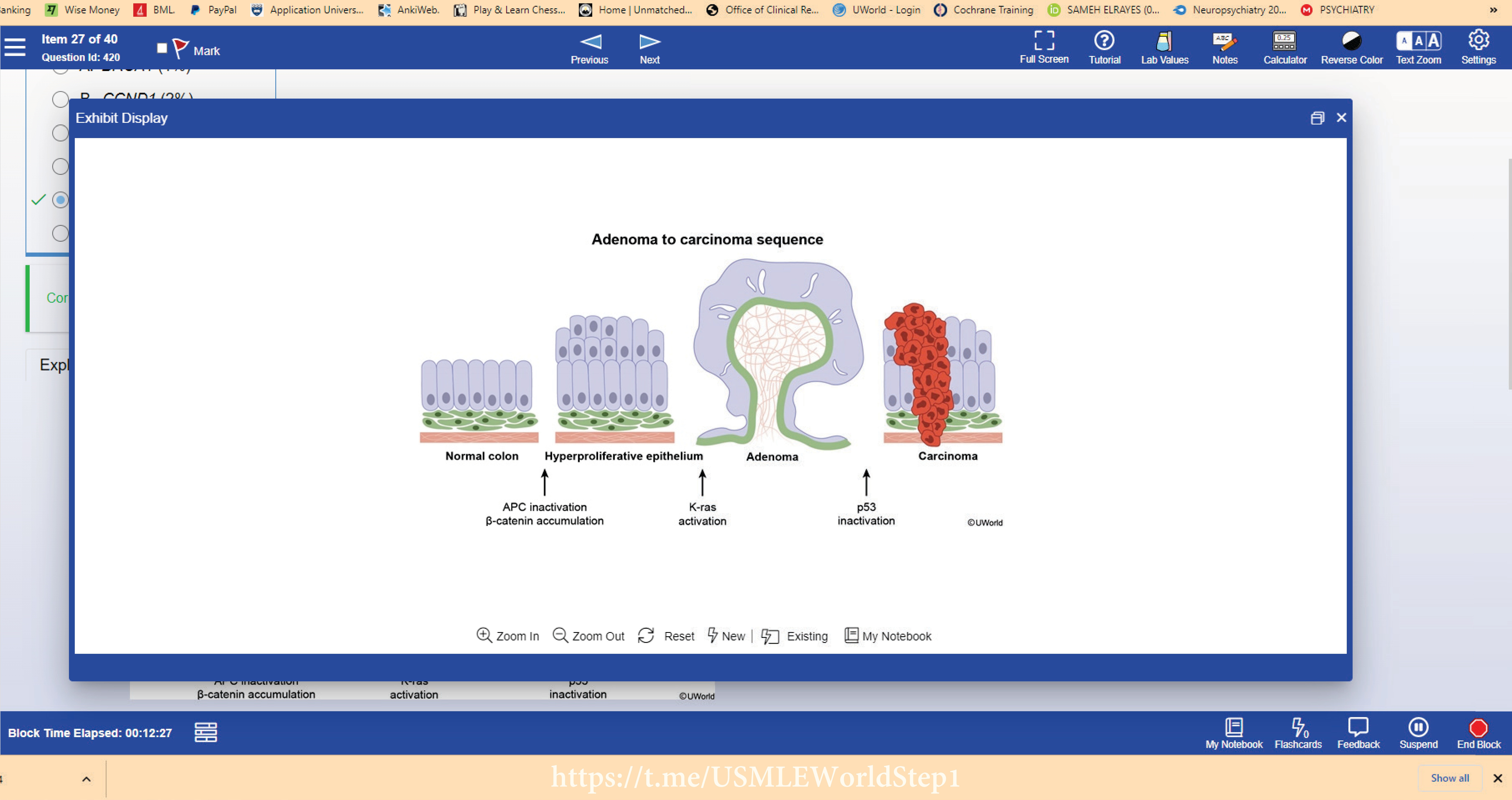
03 secs Time Spent

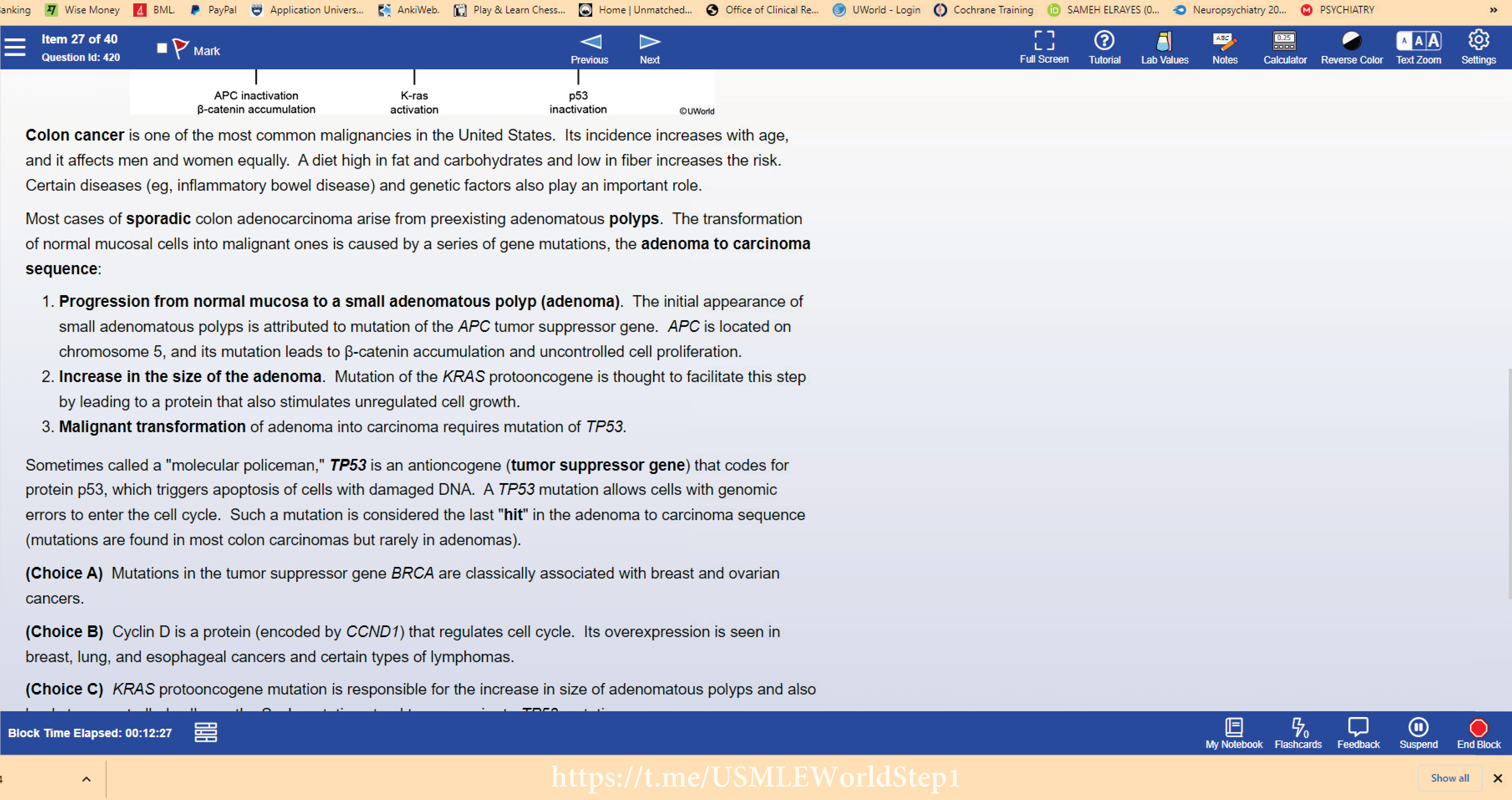
2023 Version

Explanation

Adenoma to carcinoma sequence

Block Time Elapsed: 00:12:27
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Item 27 of 40
Question Id: 420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Adenoma to carcinoma sequence
Normal colon
Hyperproliferative epithelium
Adenoma
Carcinoma
APC inactivation
β-catenin accumulation
K-ras
activation
p53
inactivation
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:27
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 27 of 40
Question Id: 420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
APC inactivation
β-catenin accumulation
K-ras
activation
p53
inactivation
©UWorld
Block Time Elapsed: 00:12:27
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Colon cancer is one of the most common malignancies in the United States. Its incidence increases with age, and it affects men and women equally. A diet high in fat and carbohydrates and low in fiber increases the risk. Certain diseases (eg, inflammatory bowel disease) and genetic factors also play an important role.

Most cases of **sporadic** colon adenocarcinoma arise from preexisting adenomatous **polyps**. The transformation of normal mucosal cells into malignant ones is caused by a series of gene mutations, the **adenoma to carcinoma sequence**:

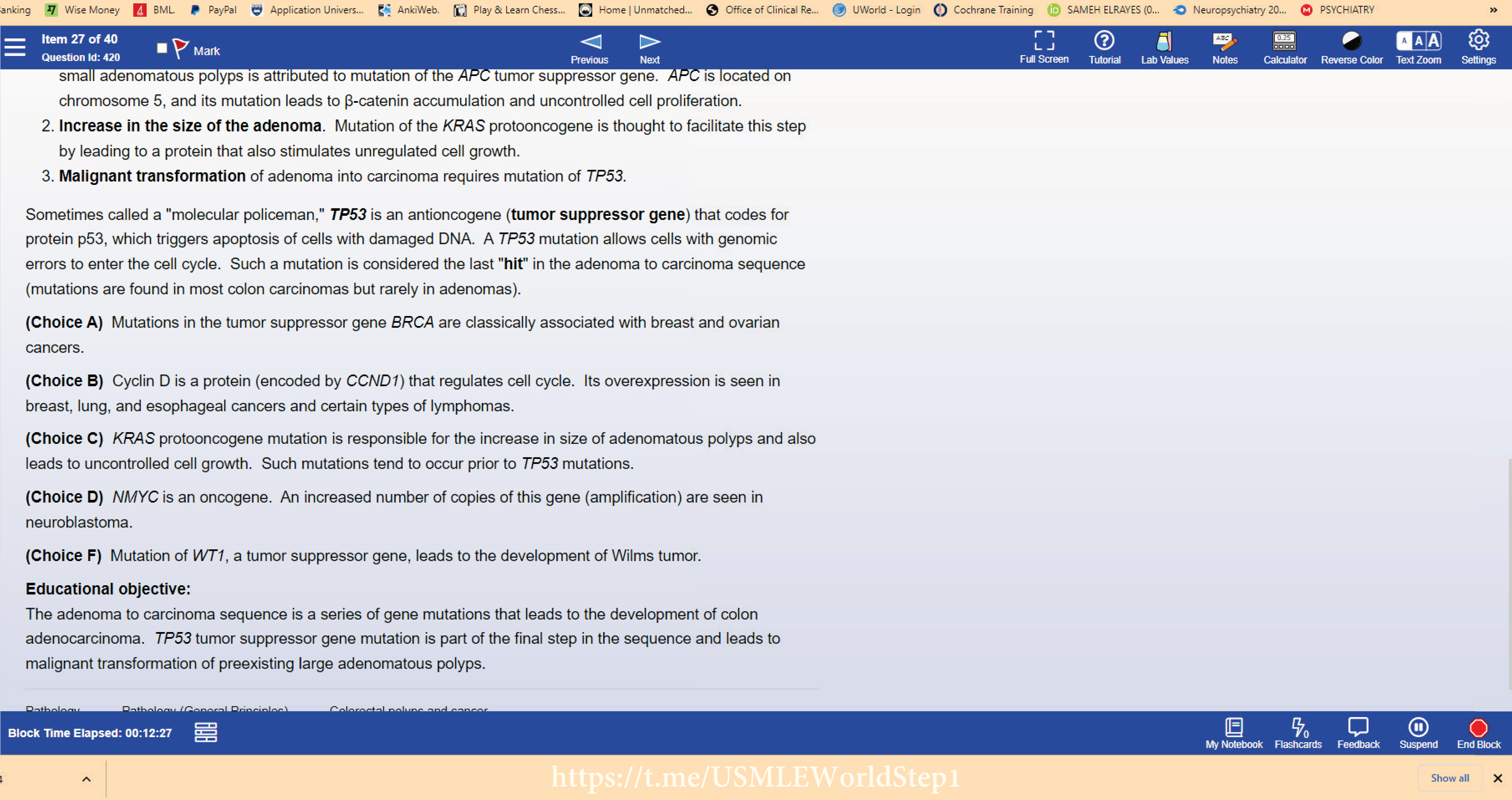
1. **Progression from normal mucosa to a small adenomatous polyp (adenoma)**. The initial appearance of small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene. *APC* is located on chromosome 5, and its mutation leads to β-catenin accumulation and uncontrolled cell proliferation.
2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step by leading to a protein that also stimulates unregulated cell growth.
3. **Malignant transformation** of adenoma into carcinoma requires mutation of *TP53*.

Sometimes called a "molecular policeman," ***TP53*** is an antioncogene (**tumor suppressor gene**) that codes for protein p53, which triggers apoptosis of cells with damaged DNA. A *TP53* mutation allows cells with genomic errors to enter the cell cycle. Such a mutation is considered the last "**hit**" in the adenoma to carcinoma sequence (mutations are found in most colon carcinomas but rarely in adenomas).

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice C) *KRAS* protooncogene mutation is responsible for the increase in size of adenomatous polyps and also


Wise Money
BML.
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 27 of 40
Question Id: 420
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene. *APC* is located on chromosome 5, and its mutation leads to β-catenin accumulation and uncontrolled cell proliferation.

2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step by leading to a protein that also stimulates unregulated cell growth.
3. **Malignant transformation** of adenoma into carcinoma requires mutation of *TP53*.

Sometimes called a "molecular policeman," ***TP53*** is an antioncogene (**tumor suppressor gene**) that codes for protein p53, which triggers apoptosis of cells with damaged DNA. A *TP53* mutation allows cells with genomic errors to enter the cell cycle. Such a mutation is considered the last "**hit**" in the adenoma to carcinoma sequence (mutations are found in most colon carcinomas but rarely in adenomas).

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice C) *KRAS* protooncogene mutation is responsible for the increase in size of adenomatous polyps and also leads to uncontrolled cell growth. Such mutations tend to occur prior to *TP53* mutations.

(Choice D) *NMYC* is an oncogene. An increased number of copies of this gene (amplification) are seen in neuroblastoma.

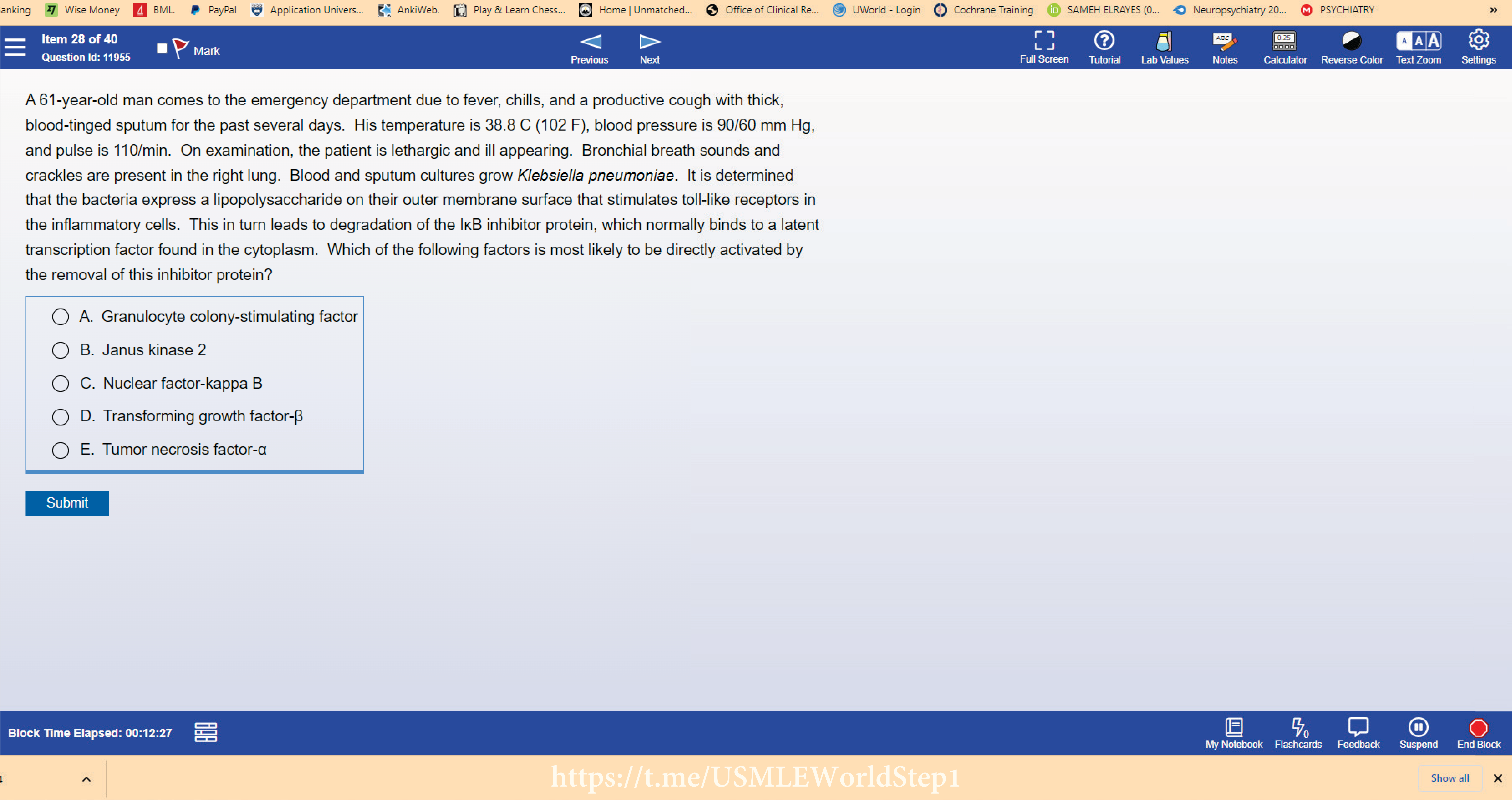
(Choice F) Mutation of *WT1*, a tumor suppressor gene, leads to the development of Wilms tumor.

Educational objective:

The adenoma to carcinoma sequence is a series of gene mutations that leads to the development of colon adenocarcinoma. *TP53* tumor suppressor gene mutation is part of the final step in the sequence and leads to malignant transformation of preexisting large adenomatous polyps.

Pathology   Pathology (General Principles)   Colorectal polyps and cancer

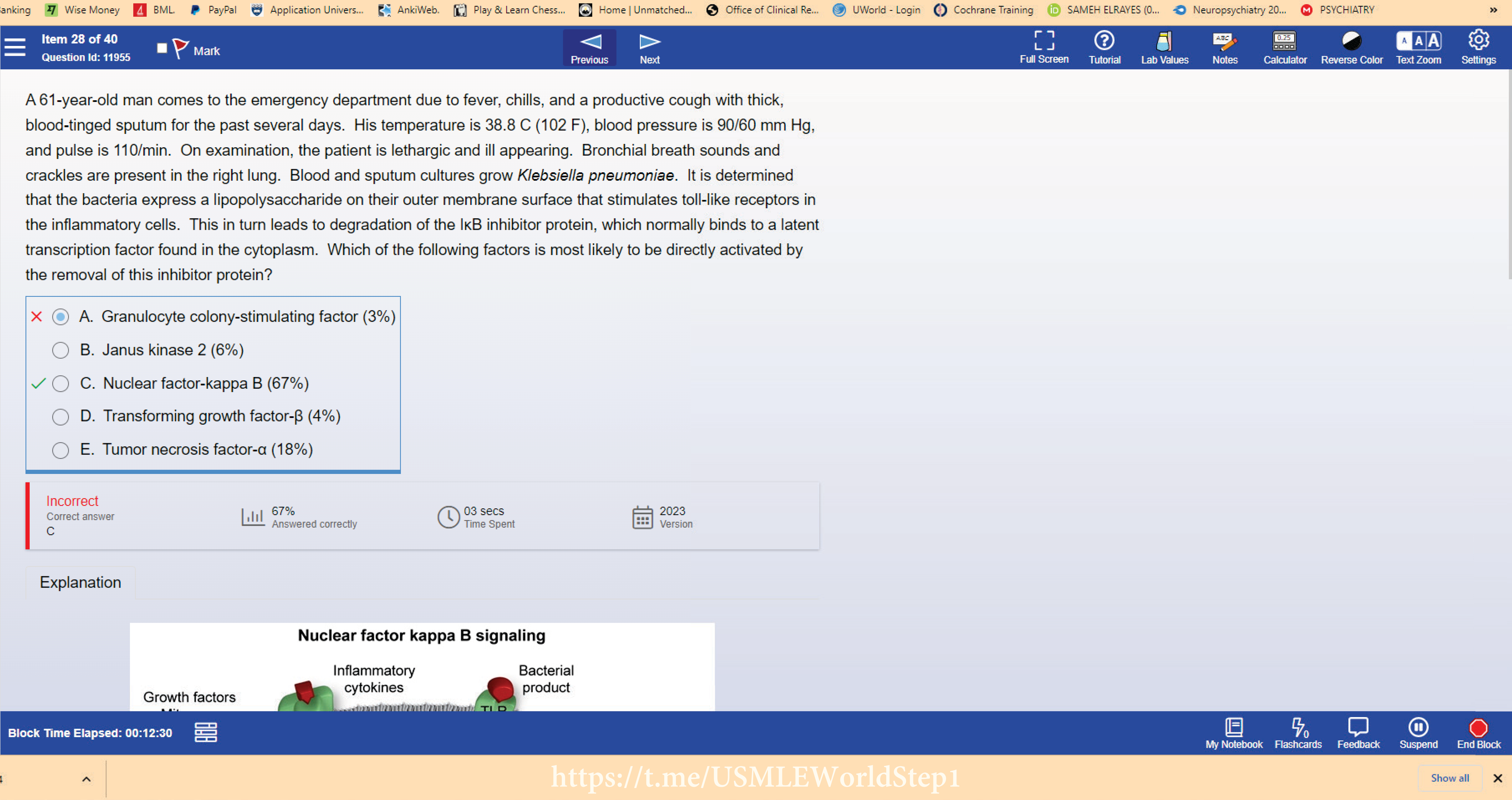
Block Time Elapsed: 00:12:27
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 28 of 40
Question Id: 11955
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 61-year-old man comes to the emergency department due to fever, chills, and a productive cough with thick, blood-tinged sputum for the past several days. His temperature is 38.8 C (102 F), blood pressure is 90/60 mm Hg, and pulse is 110/min. On examination, the patient is lethargic and ill appearing. Bronchial breath sounds and crackles are present in the right lung. Blood and sputum cultures grow *Klebsiella pneumoniae*. It is determined that the bacteria express a lipopolysaccharide on their outer membrane surface that stimulates toll-like receptors in the inflammatory cells. This in turn leads to degradation of the IκB inhibitor protein, which normally binds to a latent transcription factor found in the cytoplasm. Which of the following factors is most likely to be directly activated by the removal of this inhibitor protein?

○ A. Granulocyte colony-stimulating factor
○ B. Janus kinase 2
○ C. Nuclear factor-kappa B
○ D. Transforming growth factor-β
○ E. Tumor necrosis factor-α

Submit
Block Time Elapsed: 00:12:27
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 28 of 40
Question Id: 11955
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 61-year-old man comes to the emergency department due to fever, chills, and a productive cough with thick, blood-tinged sputum for the past several days. His temperature is 38.8 C (102 F), blood pressure is 90/60 mm Hg, and pulse is 110/min. On examination, the patient is lethargic and ill appearing. Bronchial breath sounds and crackles are present in the right lung. Blood and sputum cultures grow *Klebsiella pneumoniae*. It is determined that the bacteria express a lipopolysaccharide on their outer membrane surface that stimulates toll-like receptors in the inflammatory cells. This in turn leads to degradation of the IκB inhibitor protein, which normally binds to a latent transcription factor found in the cytoplasm. Which of the following factors is most likely to be directly activated by the removal of this inhibitor protein?

✗ ● A. Granulocyte colony-stimulating factor (3%)
○ B. Janus kinase 2 (6%)
✓ ○ C. Nuclear factor-kappa B (67%)
○ D. Transforming growth factor-β (4%)
○ E. Tumor necrosis factor-α (18%)

Incorrect
Correct answer
C

67%
Answered correctly

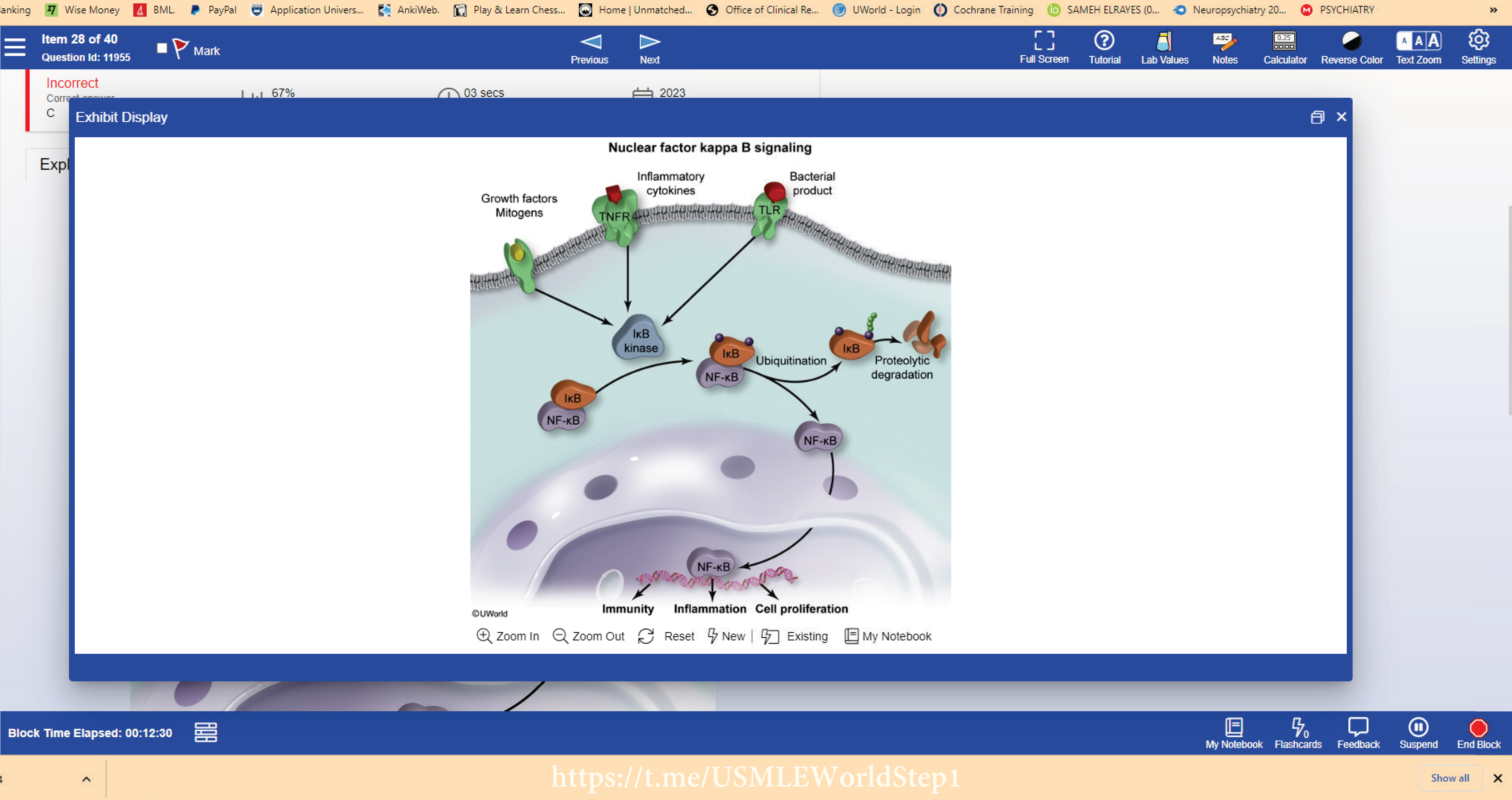
03 secs
Time Spent

2023
Version

Explanation

Nuclear factor kappa B signaling

Growth factors
Inflammatory cytokines
Bacterial product
TLR
Block Time Elapsed: 00:12:30
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Expl
Exhibit Display
Growth factors
Mitogens
Inflammatory
cytokines
TNFR
Bacterial
product
TLR
IκB
kinase
IκB
NF-κB
IκB
NF-κB
Ubiquitination
IκB
Proteolytic
degradation
NF-κB
NF-κB
Immunity
Inflammation
Cell proliferation
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 28 of 40
Question Id: 11955

Incorrect
Correct answer
C

67%

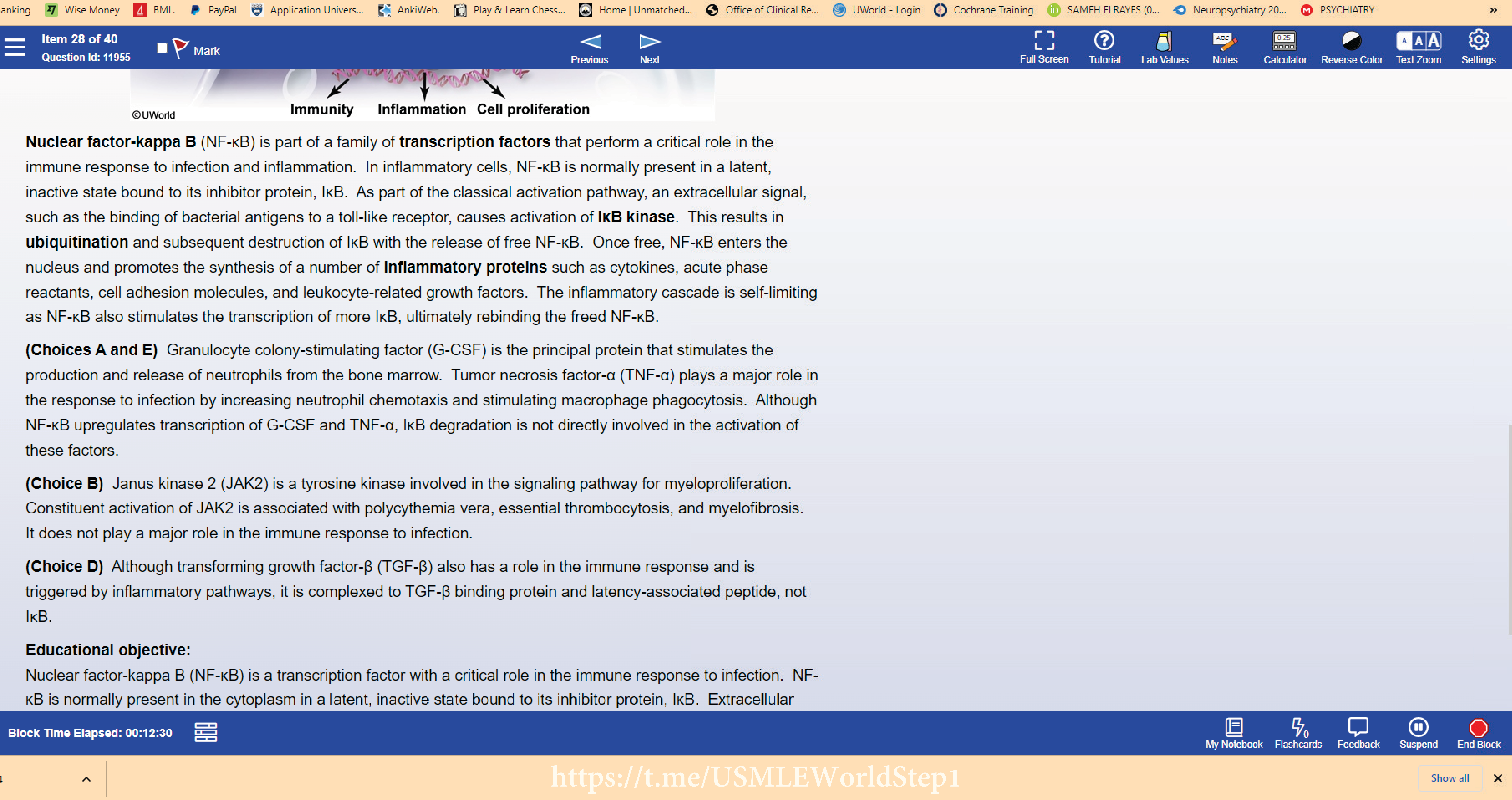
03 secs

2023

Nuclear factor kappa B signaling

Block Time Elapsed: 00:12:30

https://t.me/USMLEWorldStep1


Item 28 of 40
Question Id: 11955
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld
Immunity
Inflammation
Cell proliferation
Block Time Elapsed: 00:12:30
My Notebook
Flashcards
Feedback
Suspend
End Block

Nuclear factor-kappa B (NF-κB) is part of a family of **transcription factors** that perform a critical role in the immune response to infection and inflammation. In inflammatory cells, NF-κB is normally present in a latent, inactive state bound to its inhibitor protein, IκB. As part of the classical activation pathway, an extracellular signal, such as the binding of bacterial antigens to a toll-like receptor, causes activation of **IκB kinase**. This results in **ubiquitination** and subsequent destruction of IκB with the release of free NF-κB. Once free, NF-κB enters the nucleus and promotes the synthesis of a number of **inflammatory proteins** such as cytokines, acute phase reactants, cell adhesion molecules, and leukocyte-related growth factors. The inflammatory cascade is self-limiting as NF-κB also stimulates the transcription of more IκB, ultimately rebinding the freed NF-κB.

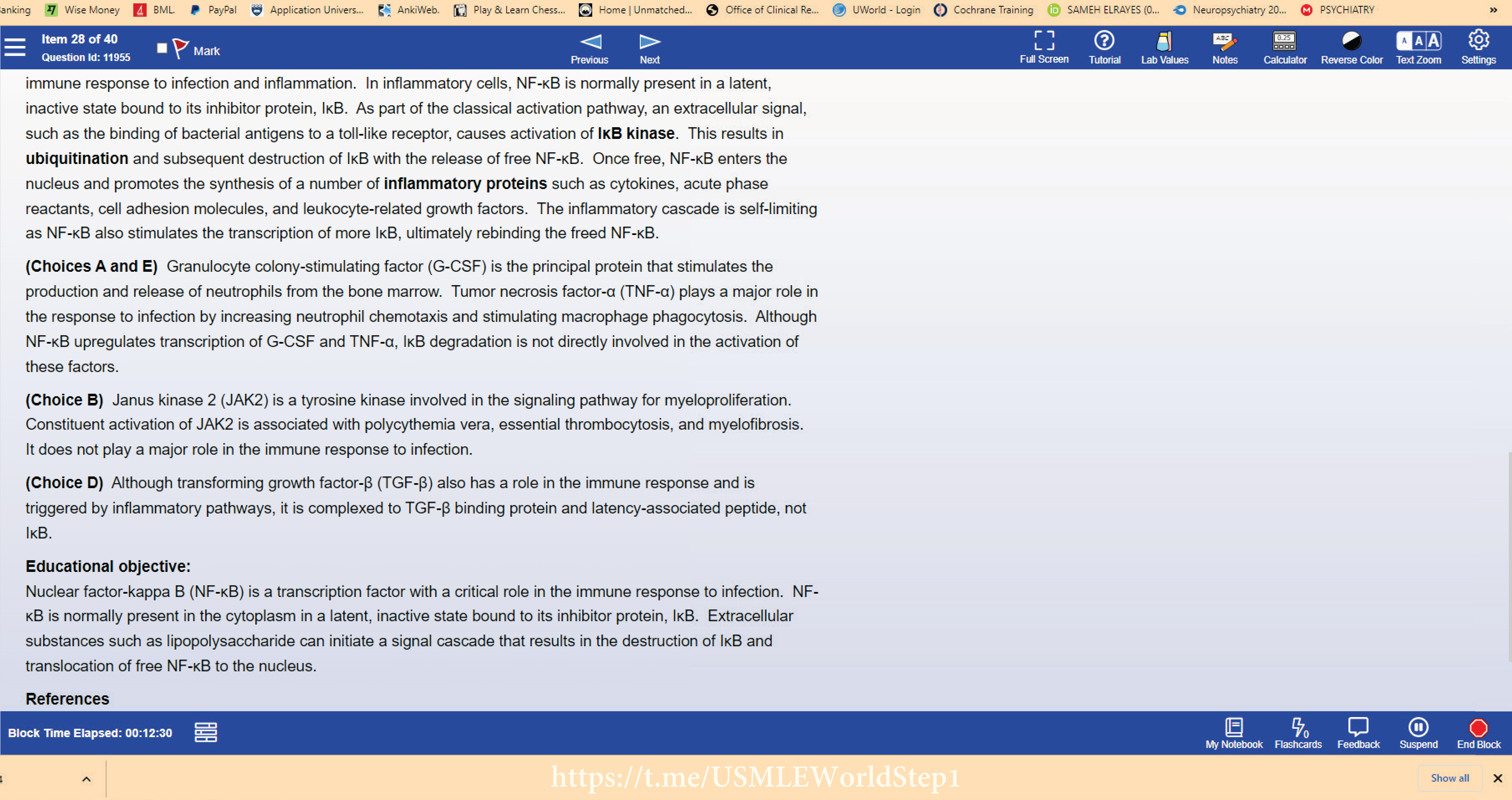
(Choices A and E) Granulocyte colony-stimulating factor (G-CSF) is the principal protein that stimulates the production and release of neutrophils from the bone marrow. Tumor necrosis factor-α (TNF-α) plays a major role in the response to infection by increasing neutrophil chemotaxis and stimulating macrophage phagocytosis. Although NF-κB upregulates transcription of G-CSF and TNF-α, IκB degradation is not directly involved in the activation of these factors.

(Choice B) Janus kinase 2 (JAK2) is a tyrosine kinase involved in the signaling pathway for myeloproliferation. Constituent activation of JAK2 is associated with polycythemia vera, essential thrombocytosis, and myelofibrosis. It does not play a major role in the immune response to infection.

(Choice D) Although transforming growth factor-β (TGF-β) also has a role in the immune response and is triggered by inflammatory pathways, it is complexed to TGF-β binding protein and latency-associated peptide, not IκB.

Educational objective:

Nuclear factor-kappa B (NF-κB) is a transcription factor with a critical role in the immune response to infection. NF-κB is normally present in the cytoplasm in a latent, inactive state bound to its inhibitor protein, IκB. Extracellular


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 28 of 40
Question Id: 11955
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:30
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

immune response to infection and inflammation. In inflammatory cells, NF-κB is normally present in a latent, inactive state bound to its inhibitor protein, IκB. As part of the classical activation pathway, an extracellular signal, such as the binding of bacterial antigens to a toll-like receptor, causes activation of **IκB kinase**. This results in **ubiquitination** and subsequent destruction of IκB with the release of free NF-κB. Once free, NF-κB enters the nucleus and promotes the synthesis of a number of **inflammatory proteins** such as cytokines, acute phase reactants, cell adhesion molecules, and leukocyte-related growth factors. The inflammatory cascade is self-limiting as NF-κB also stimulates the transcription of more IκB, ultimately rebinding the freed NF-κB.

(Choices A and E) Granulocyte colony-stimulating factor (G-CSF) is the principal protein that stimulates the production and release of neutrophils from the bone marrow. Tumor necrosis factor-α (TNF-α) plays a major role in the response to infection by increasing neutrophil chemotaxis and stimulating macrophage phagocytosis. Although NF-κB upregulates transcription of G-CSF and TNF-α, IκB degradation is not directly involved in the activation of these factors.

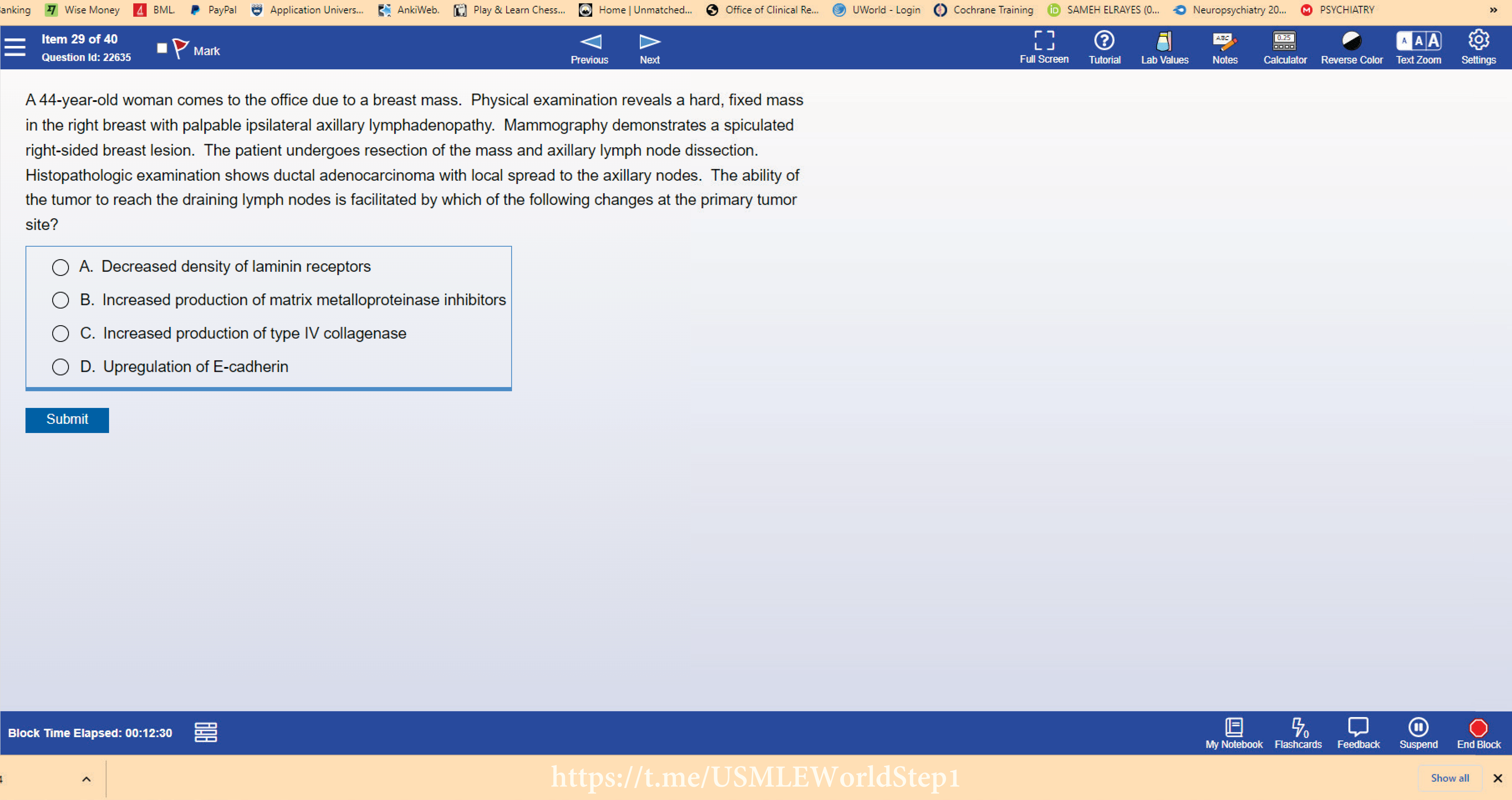
(Choice B) Janus kinase 2 (JAK2) is a tyrosine kinase involved in the signaling pathway for myeloproliferation. Constituent activation of JAK2 is associated with polycythemia vera, essential thrombocytosis, and myelofibrosis. It does not play a major role in the immune response to infection.

(Choice D) Although transforming growth factor-β (TGF-β) also has a role in the immune response and is triggered by inflammatory pathways, it is complexed to TGF-β binding protein and latency-associated peptide, not IκB.

Educational objective:

Nuclear factor-kappa B (NF-κB) is a transcription factor with a critical role in the immune response to infection. NF-κB is normally present in the cytoplasm in a latent, inactive state bound to its inhibitor protein, IκB. Extracellular substances such as lipopolysaccharide can initiate a signal cascade that results in the destruction of IκB and translocation of free NF-κB to the nucleus.

References

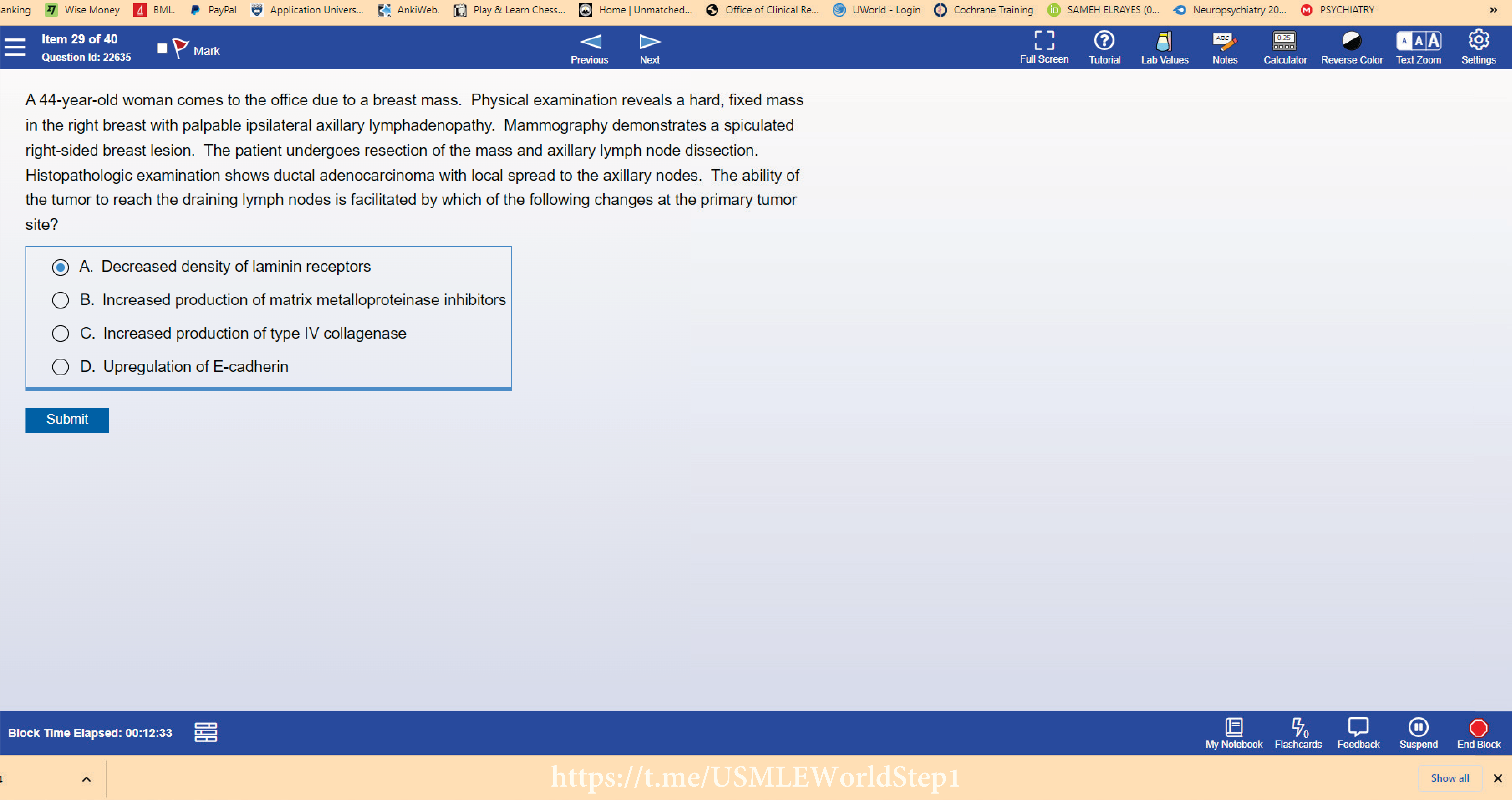

anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb.
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 29 of 40
Question Id: 22635

A 44-year-old woman comes to the office due to a breast mass. Physical examination reveals a hard, fixed mass in the right breast with palpable ipsilateral axillary lymphadenopathy. Mammography demonstrates a spiculated right-sided breast lesion. The patient undergoes resection of the mass and axillary lymph node dissection. Histopathologic examination shows ductal adenocarcinoma with local spread to the axillary nodes. The ability of the tumor to reach the draining lymph nodes is facilitated by which of the following changes at the primary tumor site?

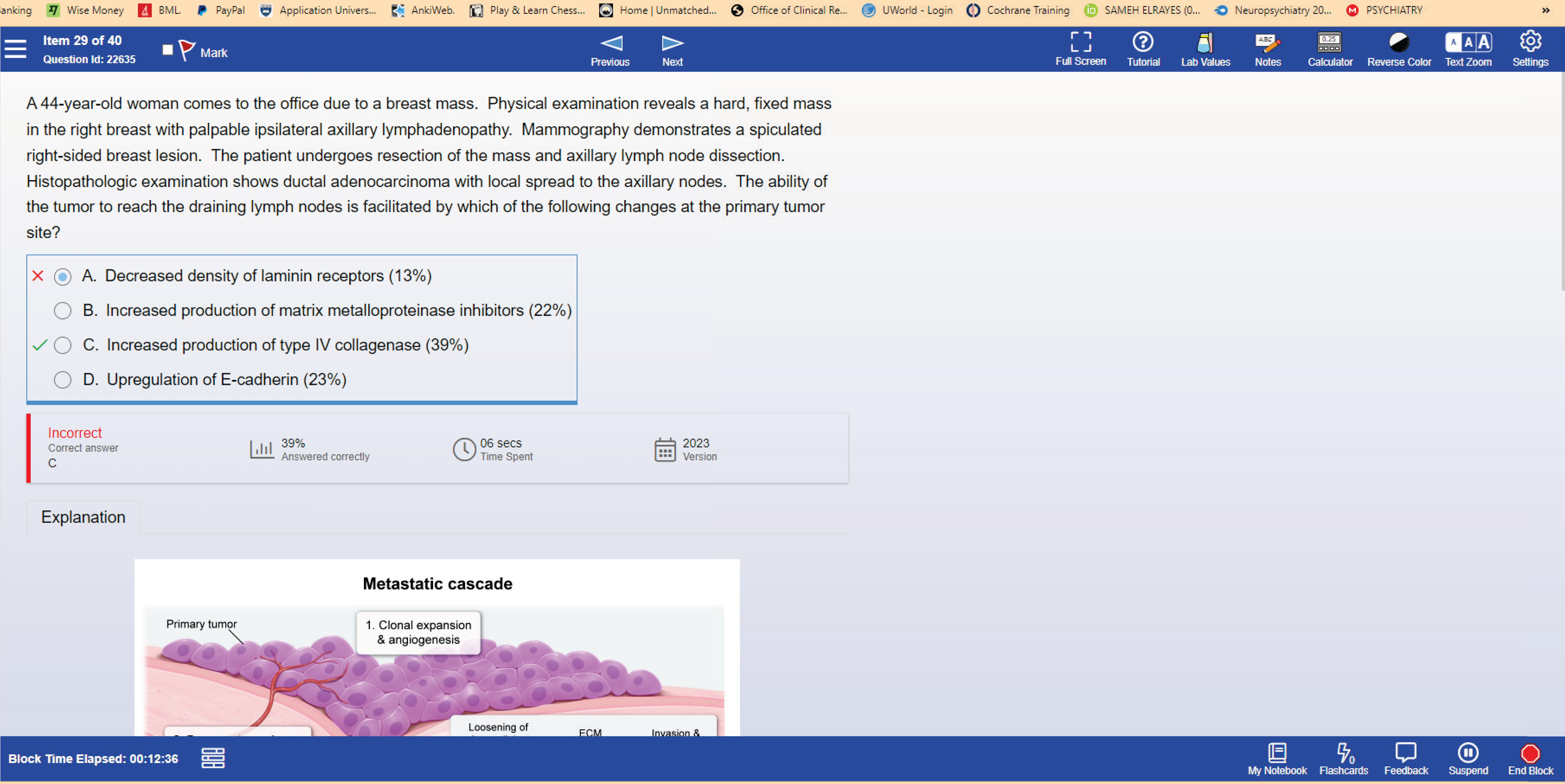
○ A. Decreased density of laminin receptors
○ B. Increased production of matrix metalloproteinase inhibitors
○ C. Increased production of type IV collagenase
○ D. Upregulation of E-cadherin

Block Time Elapsed: 00:12:30


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 29 of 40
Question Id: 22635
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
Block Time Elapsed: 00:12:33
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 44-year-old woman comes to the office due to a breast mass. Physical examination reveals a hard, fixed mass in the right breast with palpable ipsilateral axillary lymphadenopathy. Mammography demonstrates a spiculated right-sided breast lesion. The patient undergoes resection of the mass and axillary lymph node dissection. Histopathologic examination shows ductal adenocarcinoma with local spread to the axillary nodes. The ability of the tumor to reach the draining lymph nodes is facilitated by which of the following changes at the primary tumor site?

● A. Decreased density of laminin receptors
○ B. Increased production of matrix metalloproteinase inhibitors
○ C. Increased production of type IV collagenase
○ D. Upregulation of E-cadherin


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 29 of 40
Question Id: 22635
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 44-year-old woman comes to the office due to a breast mass. Physical examination reveals a hard, fixed mass in the right breast with palpable ipsilateral axillary lymphadenopathy. Mammography demonstrates a spiculated right-sided breast lesion. The patient undergoes resection of the mass and axillary lymph node dissection. Histopathologic examination shows ductal adenocarcinoma with local spread to the axillary nodes. The ability of the tumor to reach the draining lymph nodes is facilitated by which of the following changes at the primary tumor site?

✗ ● A. Decreased density of laminin receptors (13%)
○ B. Increased production of matrix metalloproteinase inhibitors (22%)
✓ ○ C. Increased production of type IV collagenase (39%)
○ D. Upregulation of E-cadherin (23%)

Incorrect
Correct answer
C

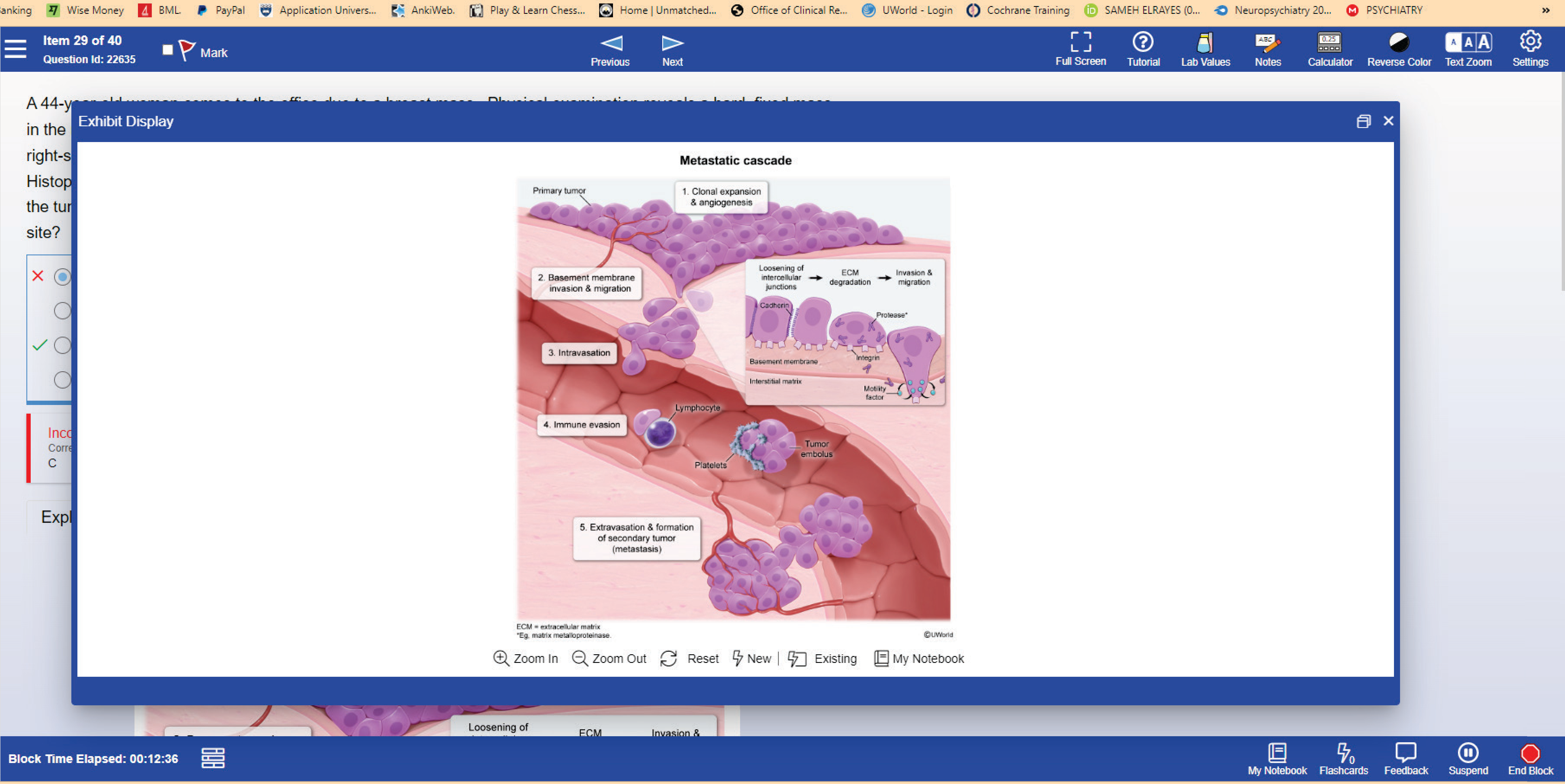
39%
Answered correctly

06 secs
Time Spent

2023
Version

Explanation

Metastatic cascade
Primary tumor
1. Clonal expansion & angiogenesis
Loosening of
ECM
Invasion &
Block Time Elapsed: 00:12:36
My Notebook
Flashcards
Feedback
Suspend
End Block


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 29 of 40
Question Id: 22635
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Primary tumor
1. Clonal expansion & angiogenesis
2. Basement membrane invasion & migration
3. Intravasation
4. Immune evasion
5. Extravasation & formation of secondary tumor (metastasis)
Loosening of intercellular junctions
ECM degradation
Invasion & migration
Cadherin
Protease*
Basement membrane
Integrin
Interstitial matrix
Motility factor
Lymphocyte
Platelets
Tumor embolus
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:12:36
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

A 44-y

in the

right-s

Histop

the tur

site?

Inco

Corre

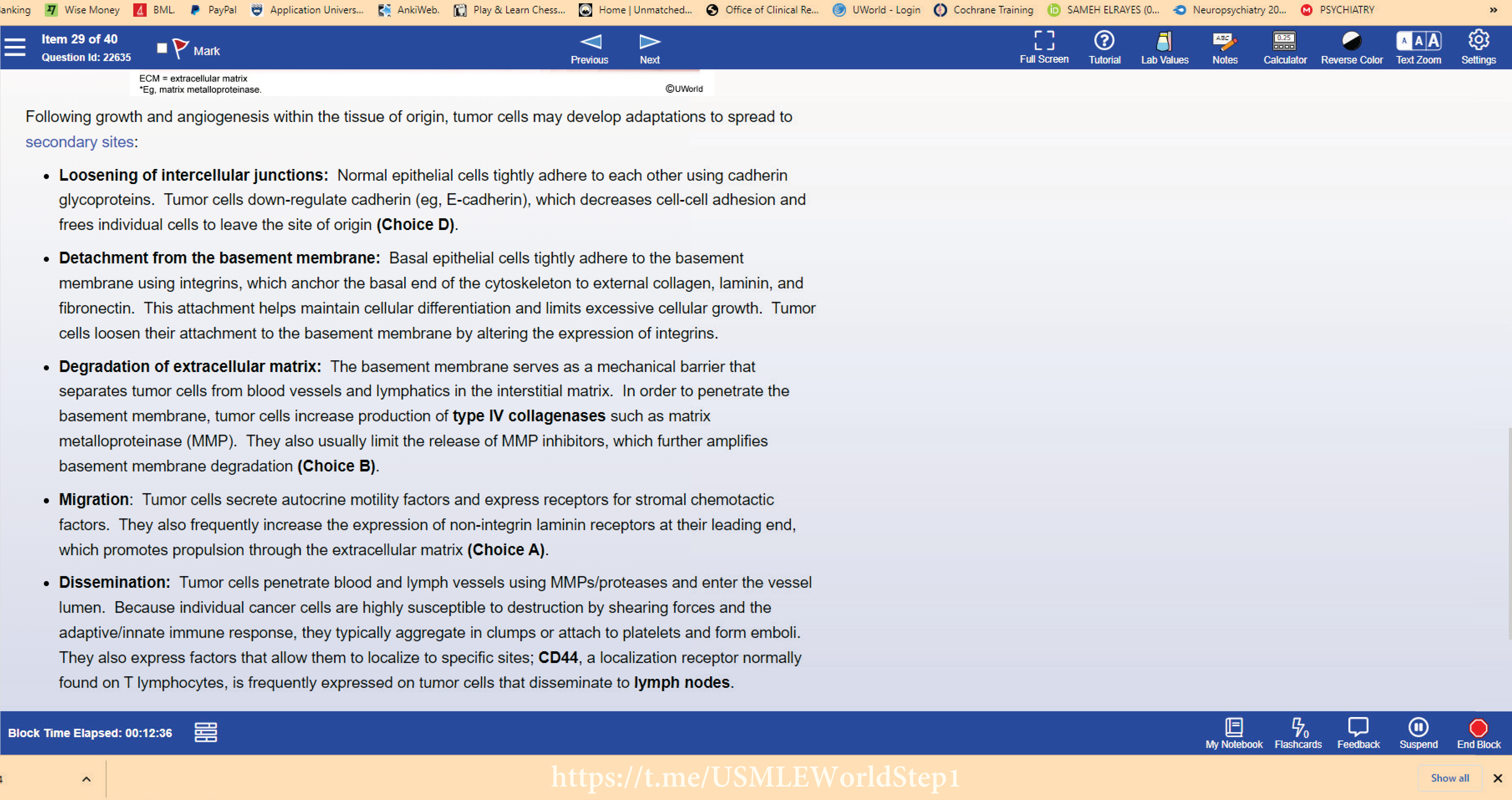
C

Expl

Metastatic cascade

ECM = extracellular matrix

*Eg, matrix metalloproteinase.


anking
Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 29 of 40
Question Id: 22635
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

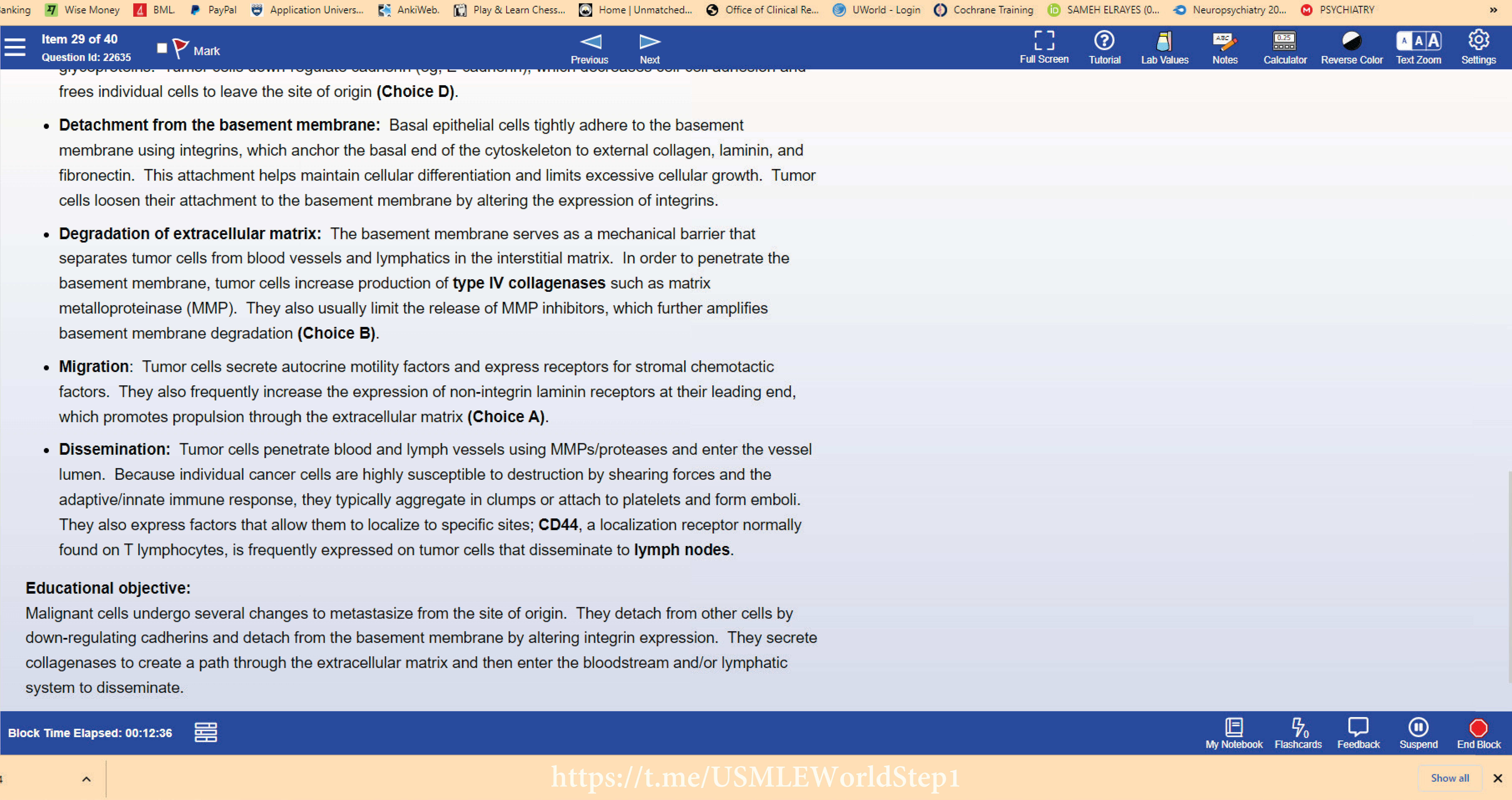
ECM = extracellular matrix
*Eg, matrix metalloproteinase.

©UWorld

Following growth and angiogenesis within the tissue of origin, tumor cells may develop adaptations to spread to secondary sites:

- **Loosening of intercellular junctions:** Normal epithelial cells tightly adhere to each other using cadherin glycoproteins. Tumor cells down-regulate cadherin (eg, E-cadherin), which decreases cell-cell adhesion and frees individual cells to leave the site of origin **(Choice D)**.
- **Detachment from the basement membrane:** Basal epithelial cells tightly adhere to the basement membrane using integrins, which anchor the basal end of the cytoskeleton to external collagen, laminin, and fibronectin. This attachment helps maintain cellular differentiation and limits excessive cellular growth. Tumor cells loosen their attachment to the basement membrane by altering the expression of integrins.
- **Degradation of extracellular matrix:** The basement membrane serves as a mechanical barrier that separates tumor cells from blood vessels and lymphatics in the interstitial matrix. In order to penetrate the basement membrane, tumor cells increase production of **type IV collagenases** such as matrix metalloproteinase (MMP). They also usually limit the release of MMP inhibitors, which further amplifies basement membrane degradation **(Choice B)**.
- **Migration**: Tumor cells secrete autocrine motility factors and express receptors for stromal chemotactic factors. They also frequently increase the expression of non-integrin laminin receptors at their leading end, which promotes propulsion through the extracellular matrix **(Choice A)**.
- **Dissemination:** Tumor cells penetrate blood and lymph vessels using MMPs/proteases and enter the vessel lumen. Because individual cancer cells are highly susceptible to destruction by shearing forces and the adaptive/innate immune response, they typically aggregate in clumps or attach to platelets and form emboli. They also express factors that allow them to localize to specific sites; **CD44**, a localization receptor normally found on T lymphocytes, is frequently expressed on tumor cells that disseminate to **lymph nodes**.

Block Time Elapsed: 00:12:36
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Wise Money
BML
PayPal
Application Univers...
AnkiWeb
Play & Learn Chess...
Home | Unmatched...
Office of Clinical Re...
UWorld - Login
Cochrane Training
SAMEH ELRAYES (0...
Neuropsychiatry 20...
PSYCHIATRY
Item 29 of 40
Question Id: 22635
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

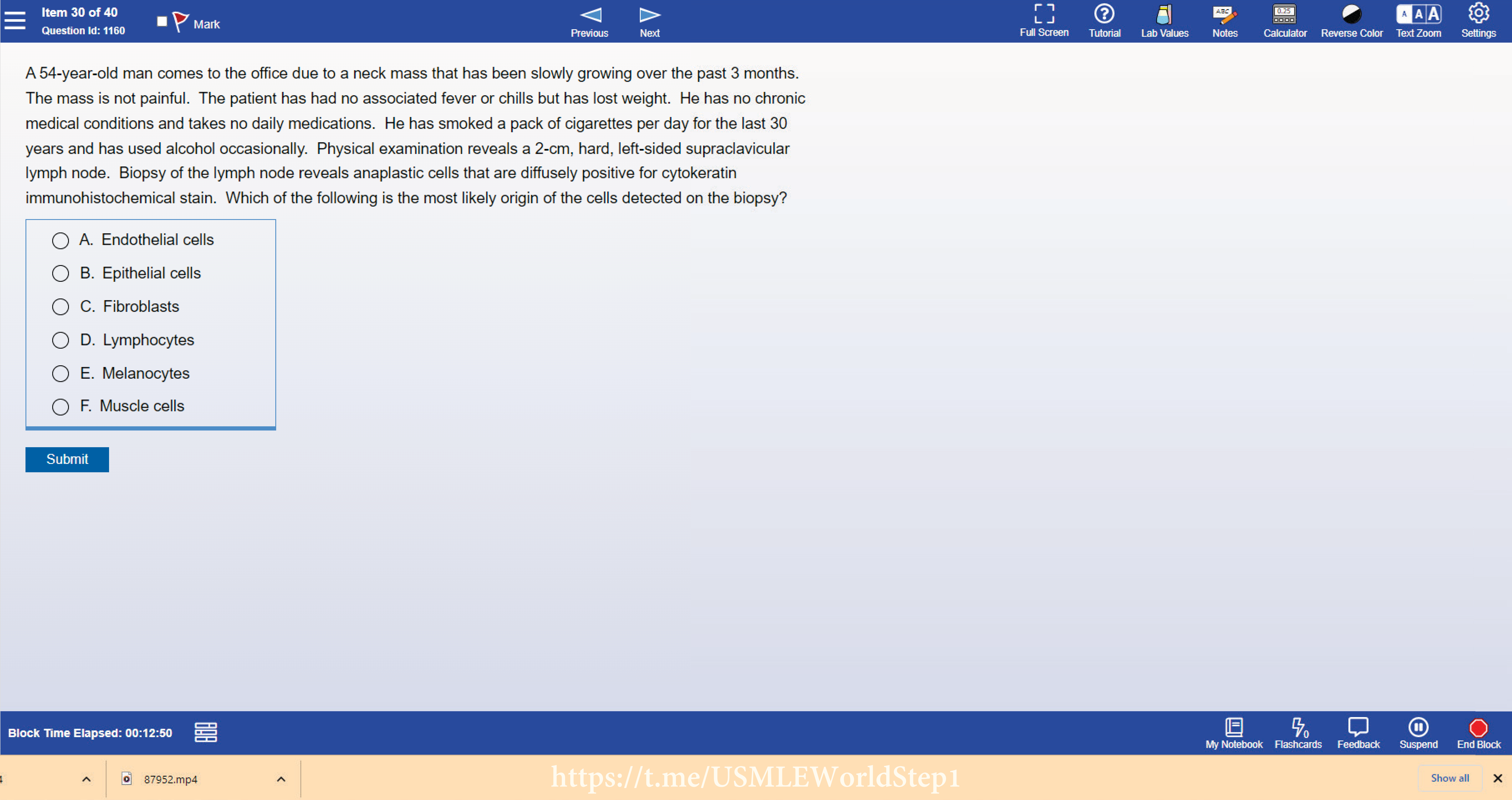
frees individual cells to leave the site of origin **(Choice D)**.

- **Detachment from the basement membrane:** Basal epithelial cells tightly adhere to the basement membrane using integrins, which anchor the basal end of the cytoskeleton to external collagen, laminin, and fibronectin. This attachment helps maintain cellular differentiation and limits excessive cellular growth. Tumor cells loosen their attachment to the basement membrane by altering the expression of integrins.
- **Degradation of extracellular matrix:** The basement membrane serves as a mechanical barrier that separates tumor cells from blood vessels and lymphatics in the interstitial matrix. In order to penetrate the basement membrane, tumor cells increase production of **type IV collagenases** such as matrix metalloproteinase (MMP). They also usually limit the release of MMP inhibitors, which further amplifies basement membrane degradation **(Choice B)**.
- **Migration**: Tumor cells secrete autocrine motility factors and express receptors for stromal chemotactic factors. They also frequently increase the expression of non-integrin laminin receptors at their leading end, which promotes propulsion through the extracellular matrix **(Choice A)**.
- **Dissemination:** Tumor cells penetrate blood and lymph vessels using MMPs/proteases and enter the vessel lumen. Because individual cancer cells are highly susceptible to destruction by shearing forces and the adaptive/innate immune response, they typically aggregate in clumps or attach to platelets and form emboli. They also express factors that allow them to localize to specific sites; **CD44**, a localization receptor normally found on T lymphocytes, is frequently expressed on tumor cells that disseminate to **lymph nodes**.

Educational objective:

Malignant cells undergo several changes to metastasize from the site of origin. They detach from other cells by down-regulating cadherins and detach from the basement membrane by altering integrin expression. They secrete collagenases to create a path through the extracellular matrix and then enter the bloodstream and/or lymphatic system to disseminate.

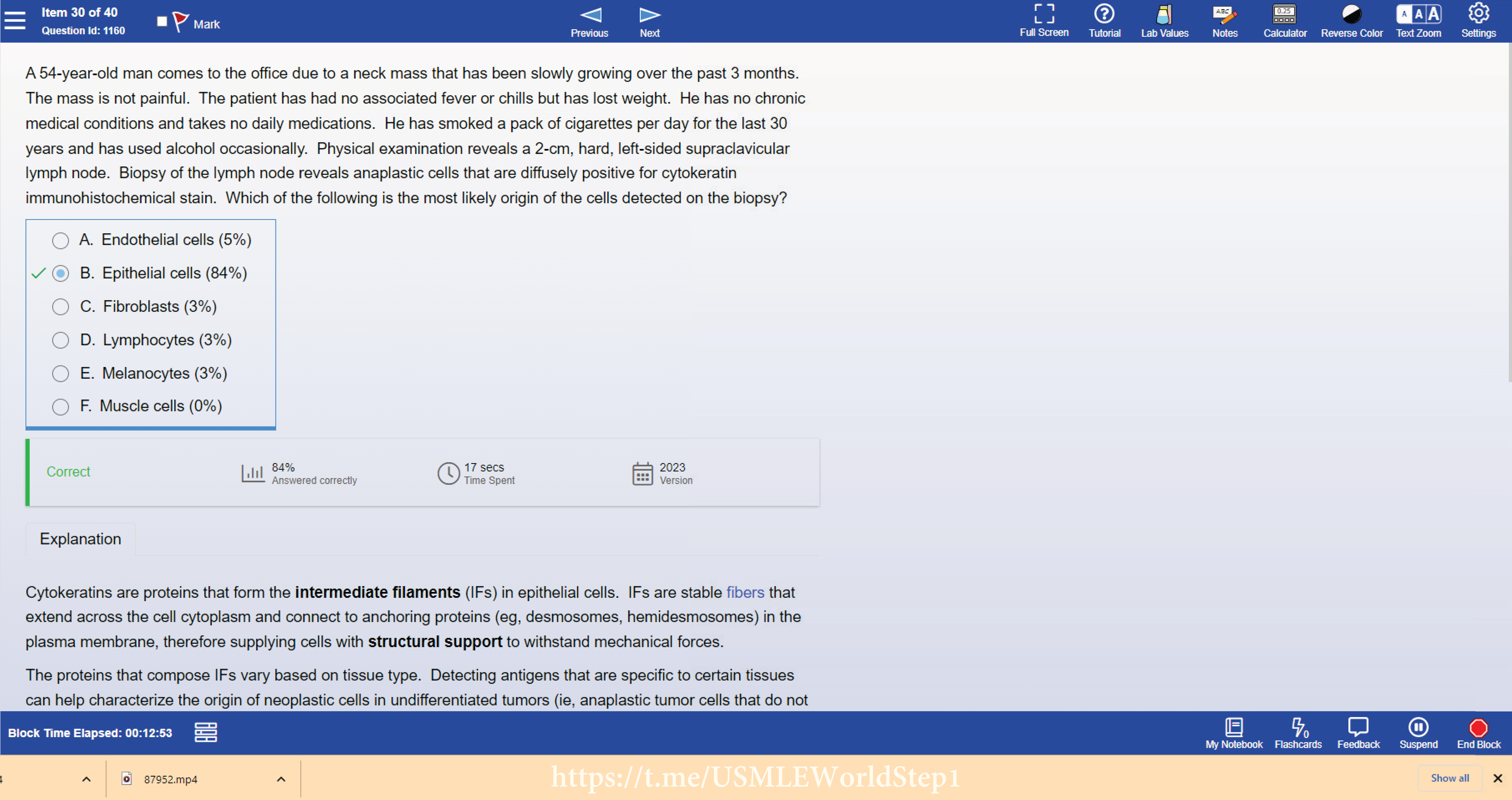
Block Time Elapsed: 00:12:36
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all


Item 30 of 40
Question Id: 1160
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 54-year-old man comes to the office due to a neck mass that has been slowly growing over the past 3 months. The mass is not painful. The patient has had no associated fever or chills but has lost weight. He has no chronic medical conditions and takes no daily medications. He has smoked a pack of cigarettes per day for the last 30 years and has used alcohol occasionally. Physical examination reveals a 2-cm, hard, left-sided supraclavicular lymph node. Biopsy of the lymph node reveals anaplastic cells that are diffusely positive for cytokeratin immunohistochemical stain. Which of the following is the most likely origin of the cells detected on the biopsy?

○ A. Endothelial cells
○ B. Epithelial cells
○ C. Fibroblasts
○ D. Lymphocytes
○ E. Melanocytes
○ F. Muscle cells

Submit
Block Time Elapsed: 00:12:50
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 30 of 40
Question Id: 1160
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 54-year-old man comes to the office due to a neck mass that has been slowly growing over the past 3 months. The mass is not painful. The patient has had no associated fever or chills but has lost weight. He has no chronic medical conditions and takes no daily medications. He has smoked a pack of cigarettes per day for the last 30 years and has used alcohol occasionally. Physical examination reveals a 2-cm, hard, left-sided supraclavicular lymph node. Biopsy of the lymph node reveals anaplastic cells that are diffusely positive for cytokeratin immunohistochemical stain. Which of the following is the most likely origin of the cells detected on the biopsy?

○ A. Endothelial cells (5%)

✓ ● B. Epithelial cells (84%)

○ C. Fibroblasts (3%)

○ D. Lymphocytes (3%)

○ E. Melanocytes (3%)

○ F. Muscle cells (0%)

Correct

84%
Answered correctly

17 secs
Time Spent

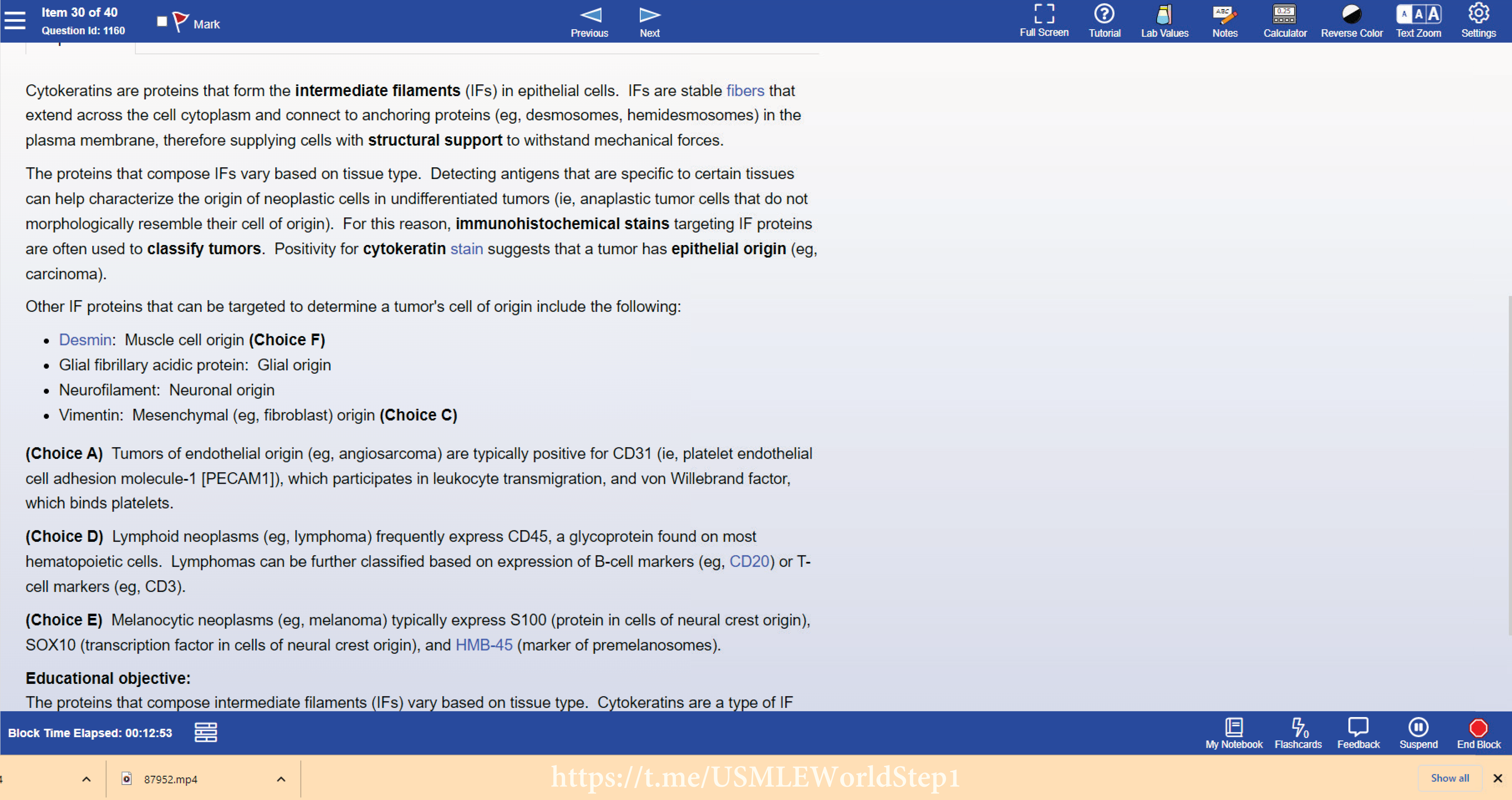
2023
Version

Explanation

Cytokeratins are proteins that form the **intermediate filaments** (IFs) in epithelial cells. IFs are stable fibers that extend across the cell cytoplasm and connect to anchoring proteins (eg, desmosomes, hemidesmosomes) in the plasma membrane, therefore supplying cells with **structural support** to withstand mechanical forces.

The proteins that compose IFs vary based on tissue type. Detecting antigens that are specific to certain tissues can help characterize the origin of neoplastic cells in undifferentiated tumors (ie, anaplastic tumor cells that do not

Block Time Elapsed: 00:12:53
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 30 of 40
Question Id: 1160
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:12:53
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Cytokeratins are proteins that form the **intermediate filaments** (IFs) in epithelial cells. IFs are stable fibers that extend across the cell cytoplasm and connect to anchoring proteins (eg, desmosomes, hemidesmosomes) in the plasma membrane, therefore supplying cells with **structural support** to withstand mechanical forces.

The proteins that compose IFs vary based on tissue type. Detecting antigens that are specific to certain tissues can help characterize the origin of neoplastic cells in undifferentiated tumors (ie, anaplastic tumor cells that do not morphologically resemble their cell of origin). For this reason, **immunohistochemical stains** targeting IF proteins are often used to **classify tumors**. Positivity for **cytokeratin** stain suggests that a tumor has **epithelial origin** (eg, carcinoma).

Other IF proteins that can be targeted to determine a tumor's cell of origin include the following:

- Desmin: Muscle cell origin **(Choice F)**
- Glial fibrillary acidic protein: Glial origin
- Neurofilament: Neuronal origin
- Vimentin: Mesenchymal (eg, fibroblast) origin **(Choice C)**

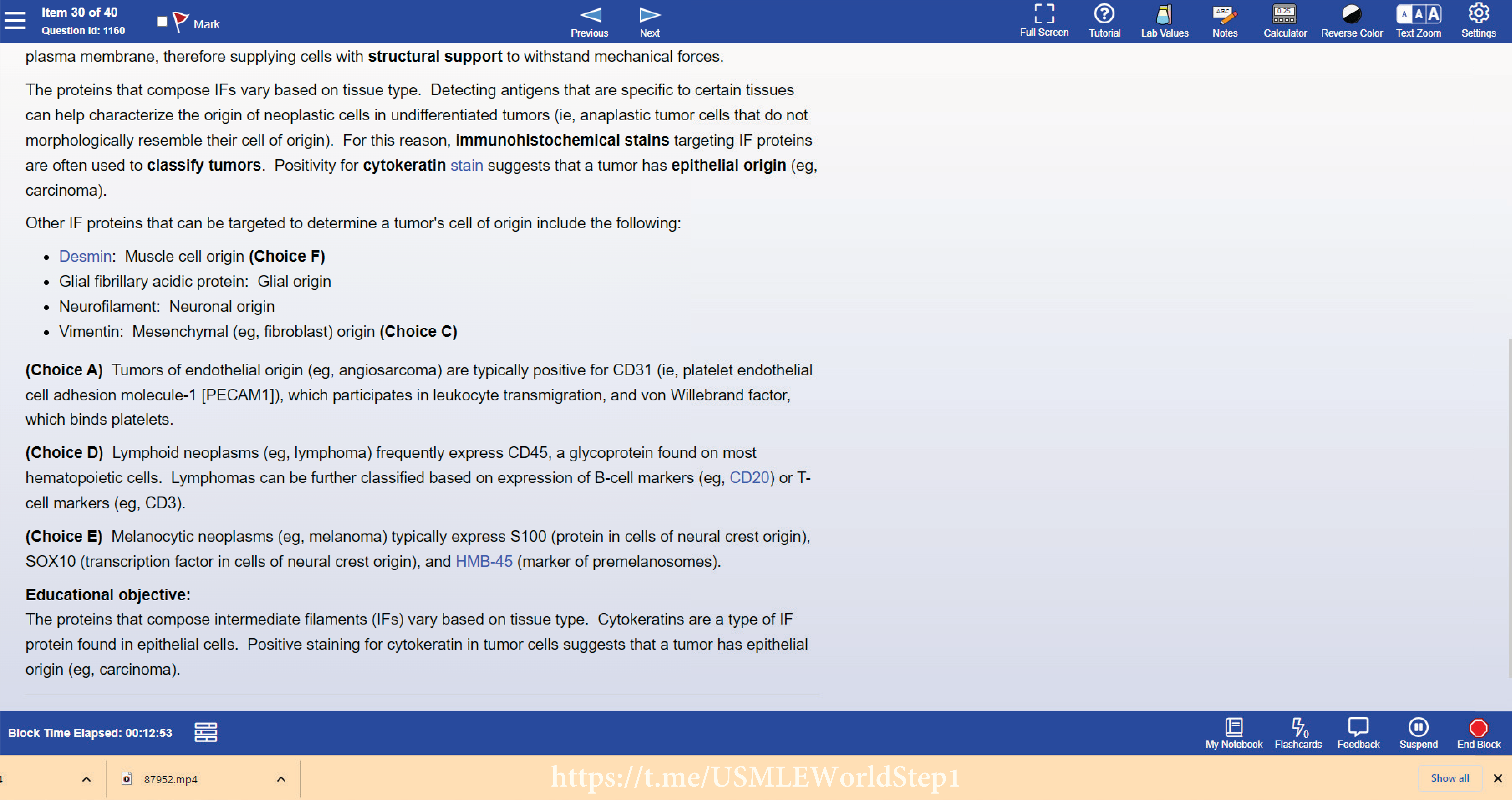
(Choice A) Tumors of endothelial origin (eg, angiosarcoma) are typically positive for CD31 (ie, platelet endothelial cell adhesion molecule-1 [PECAM1]), which participates in leukocyte transmigration, and von Willebrand factor, which binds platelets.

(Choice D) Lymphoid neoplasms (eg, lymphoma) frequently express CD45, a glycoprotein found on most hematopoietic cells. Lymphomas can be further classified based on expression of B-cell markers (eg, CD20) or T-cell markers (eg, CD3).

(Choice E) Melanocytic neoplasms (eg, melanoma) typically express S100 (protein in cells of neural crest origin), SOX10 (transcription factor in cells of neural crest origin), and HMB-45 (marker of premelanosomes).

Educational objective:

The proteins that compose intermediate filaments (IFs) vary based on tissue type. Cytokeratins are a type of IF


Item 30 of 40
Question Id: 1160
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

plasma membrane, therefore supplying cells with **structural support** to withstand mechanical forces.

The proteins that compose IFs vary based on tissue type. Detecting antigens that are specific to certain tissues can help characterize the origin of neoplastic cells in undifferentiated tumors (ie, anaplastic tumor cells that do not morphologically resemble their cell of origin). For this reason, **immunohistochemical stains** targeting IF proteins are often used to **classify tumors**. Positivity for **cytokeratin** stain suggests that a tumor has **epithelial origin** (eg, carcinoma).

Other IF proteins that can be targeted to determine a tumor's cell of origin include the following:

- Desmin: Muscle cell origin **(Choice F)**
- Glial fibrillary acidic protein: Glial origin
- Neurofilament: Neuronal origin
- Vimentin: Mesenchymal (eg, fibroblast) origin **(Choice C)**

(Choice A) Tumors of endothelial origin (eg, angiosarcoma) are typically positive for CD31 (ie, platelet endothelial cell adhesion molecule-1 [PECAM1]), which participates in leukocyte transmigration, and von Willebrand factor, which binds platelets.

(Choice D) Lymphoid neoplasms (eg, lymphoma) frequently express CD45, a glycoprotein found on most hematopoietic cells. Lymphomas can be further classified based on expression of B-cell markers (eg, CD20) or T-cell markers (eg, CD3).

(Choice E) Melanocytic neoplasms (eg, melanoma) typically express S100 (protein in cells of neural crest origin), SOX10 (transcription factor in cells of neural crest origin), and HMB-45 (marker of premelanosomes).

Educational objective:
The proteins that compose intermediate filaments (IFs) vary based on tissue type. Cytokeratins are a type of IF protein found in epithelial cells. Positive staining for cytokeratin in tumor cells suggests that a tumor has epithelial origin (eg, carcinoma).

Block Time Elapsed: 00:12:53
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Correct

84% Answered correctly

17 secs Time Spent

2023 Version

Expl

Cytoke
extenc
plasm

The pr
can he
morph
are oft
carcin

Other

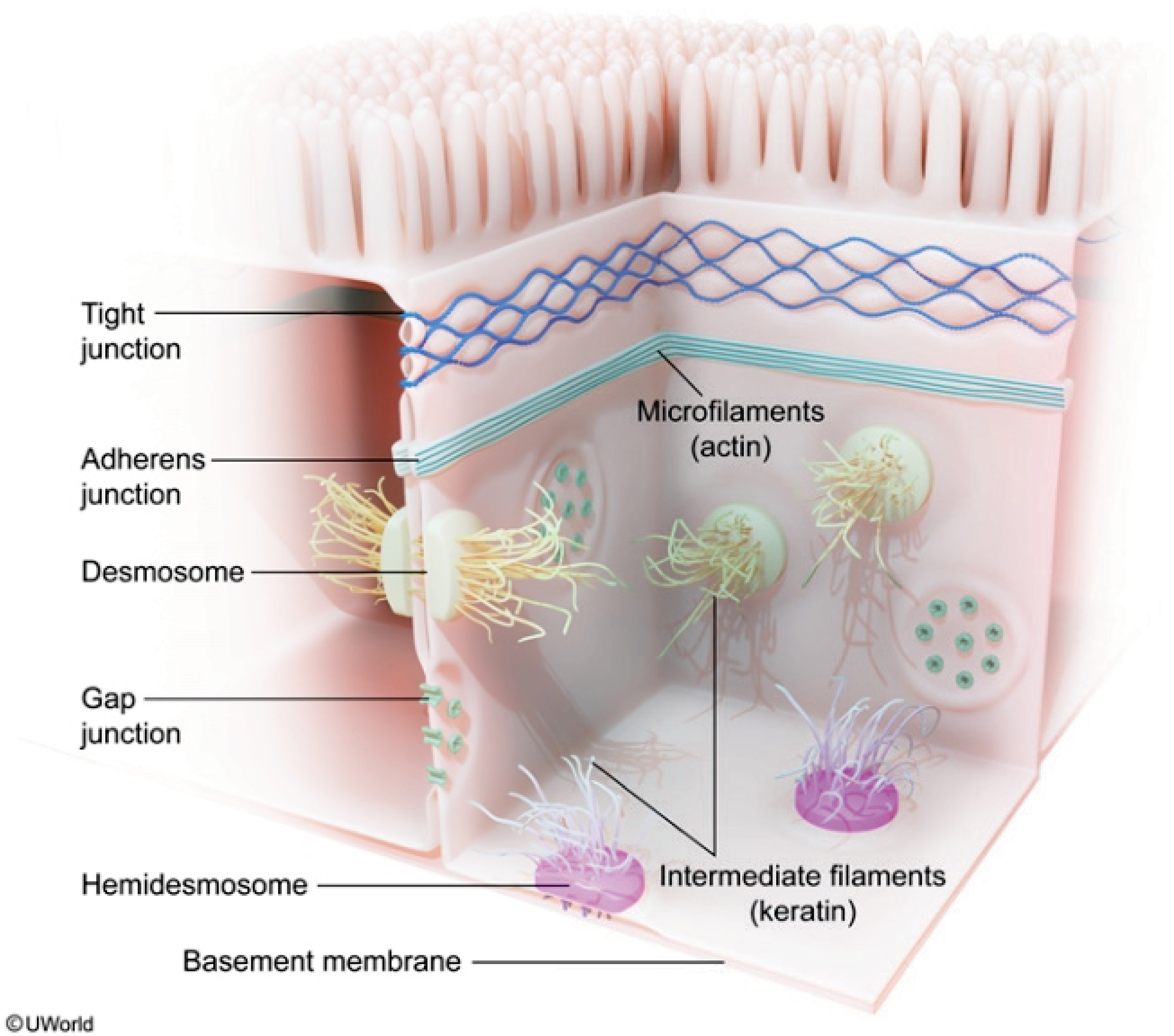
- D
- G
- N
- V

(Choi
cell ad
which

(Choi
hemat
cell ma

Exhibit Display

Cell junctions


Tight junction
Adherens junction
Desmosome
Gap junction
Hemidesmosome
Basement membrane
Microfilaments (actin)
Intermediate filaments (keratin)

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

(Choice E) Melanocytic neoplasms (eg, melanoma) typically express S100 (protein in cells of neural crest origin),

87952.mp4

Show all

Correct

84%
Answered correctly

17 secs
Time Spent

2023
Version

Exhibit Display

Expl

Cytoke
extenc
plasma

The pr
can he
morph
are oft
carcin

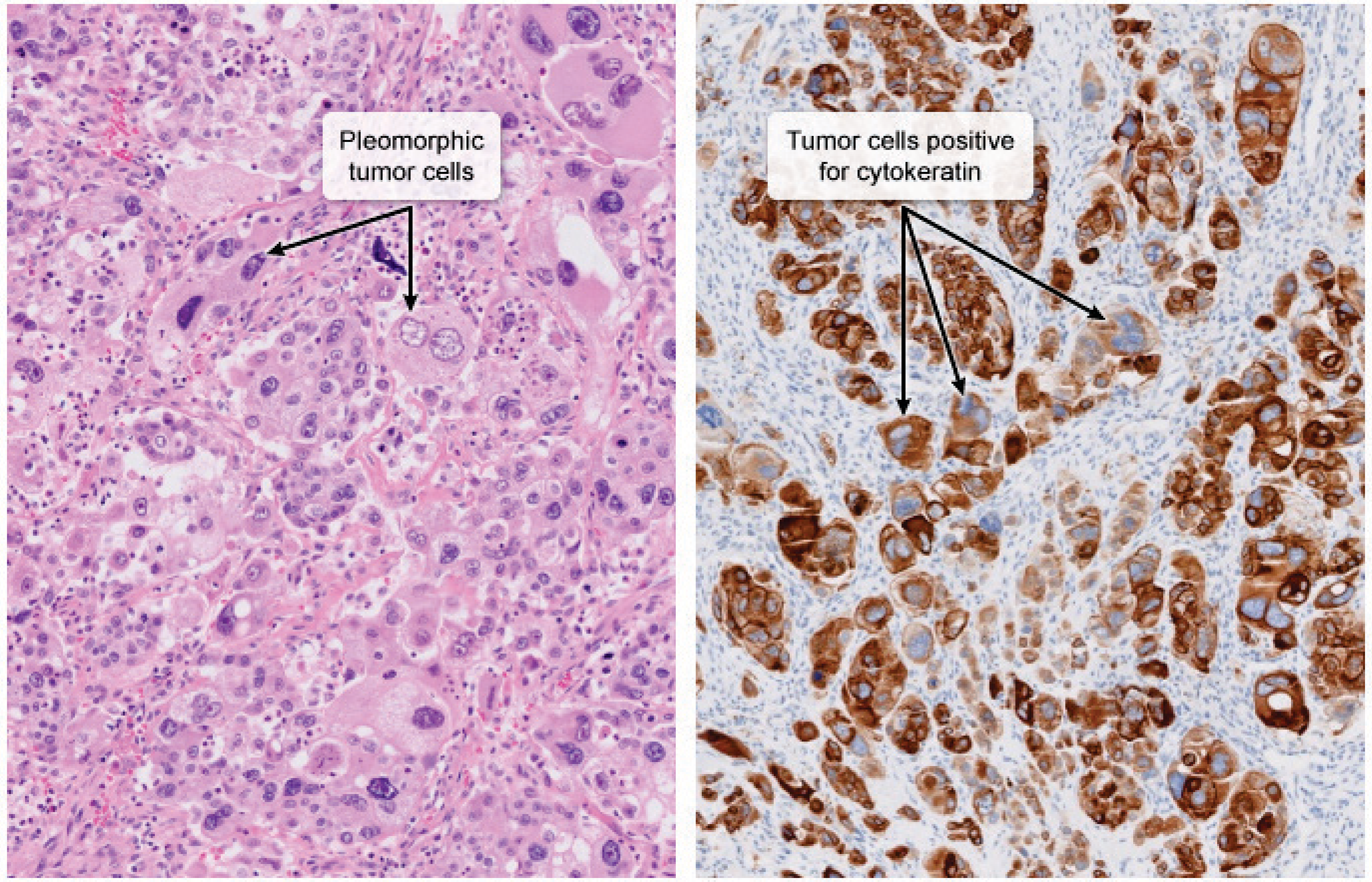
Other

- D
- G
- N
- V

(Choi
cell ad
which

(Choi
hemat
cell ma

Carcinoma


Pleomorphic tumor cells
Tumor cells positive for cytokeratin

Hematoxylin & eosin stain

Cytokeratin stain (IF protein in epithelial cells)

IF = intermediate filament.

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

(Choice E) Melanocytic neoplasms (eg, melanoma) typically express S100 (protein in cells of neural crest origin),

87952.mp4
Show all

Correct

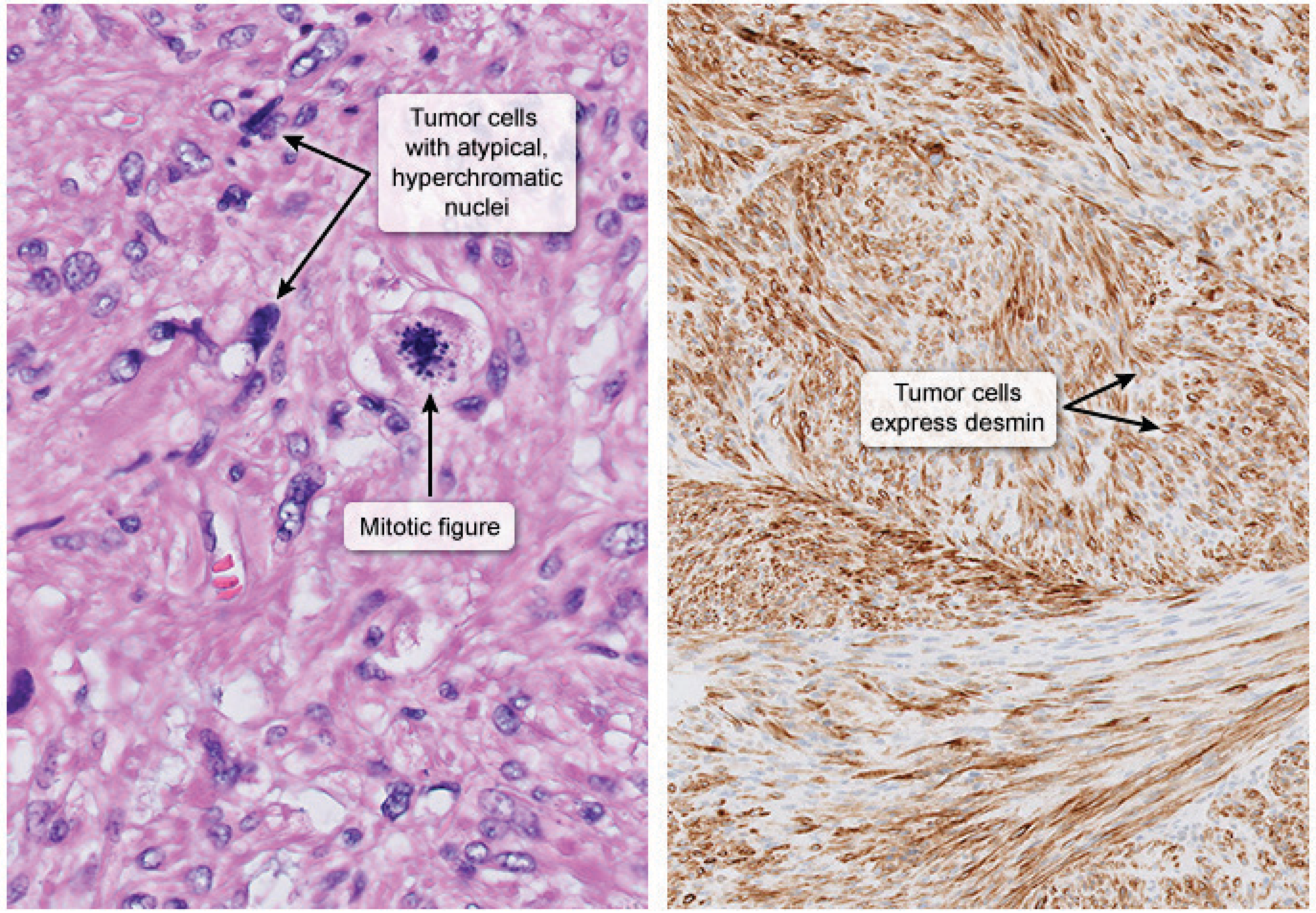
84%
Answered correctly

17 secs
Time Spent

2023
Version

Exhibit Display

Leiomyosarcoma


Tumor cells with atypical, hyperchromatic nuclei
Mitotic figure
Tumor cells express desmin

Hematoxylin & eosin stain

Desmin stain (IF protein in muscle cells)

IF = intermediate filament.

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Expl

Cytoke
extenc
plasm

The pr
can he
morph
are oft
carcin

Other

- D
- G
- N
- V

(Choi
cell ad
which

(Choi
hemat
cell m

(Choice E) Melanocytic neoplasms (eg, melanoma) typically express S100 (protein in cells of neural crest origin),

87952.mp4
Show all

can help characterize the origin of neoplastic cells in undifferentiated tumors (ie, anaplastic tumor cells that do not morph

are oft

carcin

Other

- D
- G
- N
- V

(Choi
cell ad
which

(Choi
hemat
cell ma

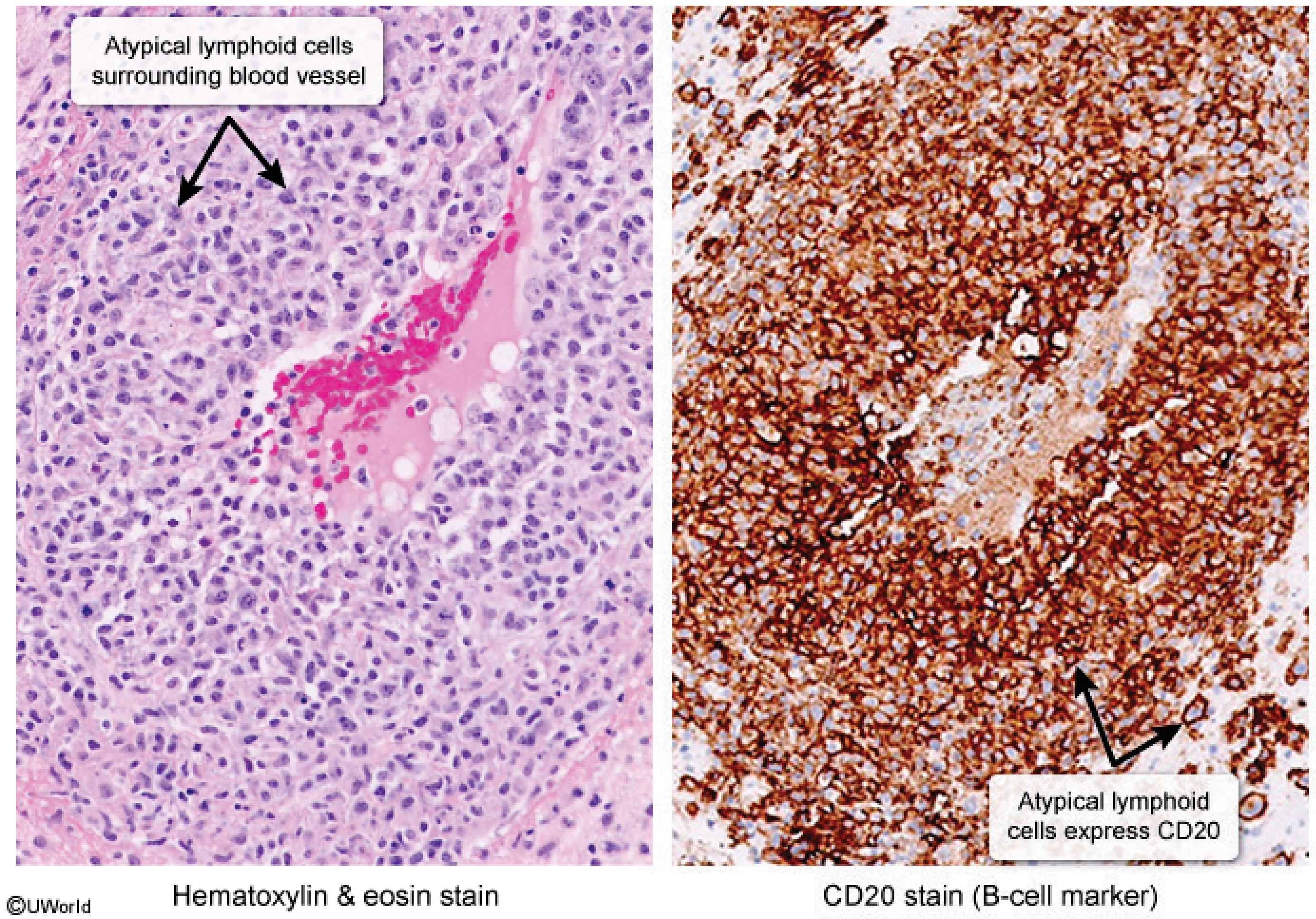
(Choi
SOX1

Educa
The pr
protei
origin

Patholog
Subject

Exhibit Display

Primary central nervous system lymphoma


Atypical lymphoid cells surrounding blood vessel
Atypical lymphoid cells express CD20
©UWorld

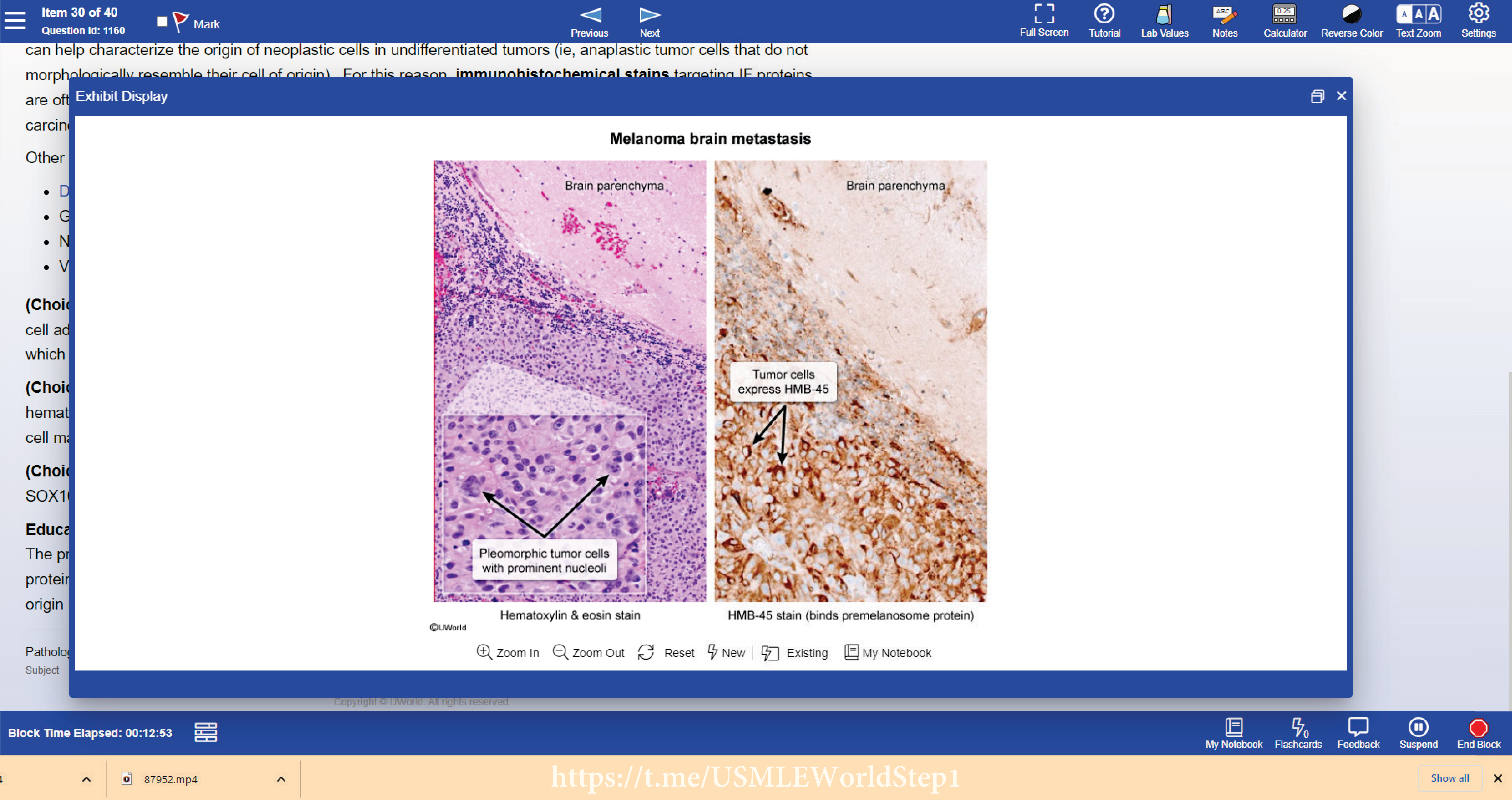
Hematoxylin & eosin stain

CD20 stain (B-cell marker)

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Copyright © UWorld. All rights reserved.

87952.mp4
Show all


Item 30 of 40
Question Id: 1160
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

can help characterize the origin of neoplastic cells in undifferentiated tumors (ie, anaplastic tumor cells that do not morphologically resemble their cell of origin). For this reason, **immunohistochemical stains** targeting IF proteins

are oft

carcin

Other

- D
- G
- N
- V

(Choi

cell ad

which

(Choi

hemat

cell ma

(Choi

SOX1

Educa

The pr

protei

origin

Patholog

Subject

Exhibit Display

Melanoma brain metastasis

Brain parenchyma
Pleomorphic tumor cells with prominent nucleoli
Brain parenchyma
Tumor cells express HMB-45

Hematoxylin & eosin stain

HMB-45 stain (binds premelanosome protein)

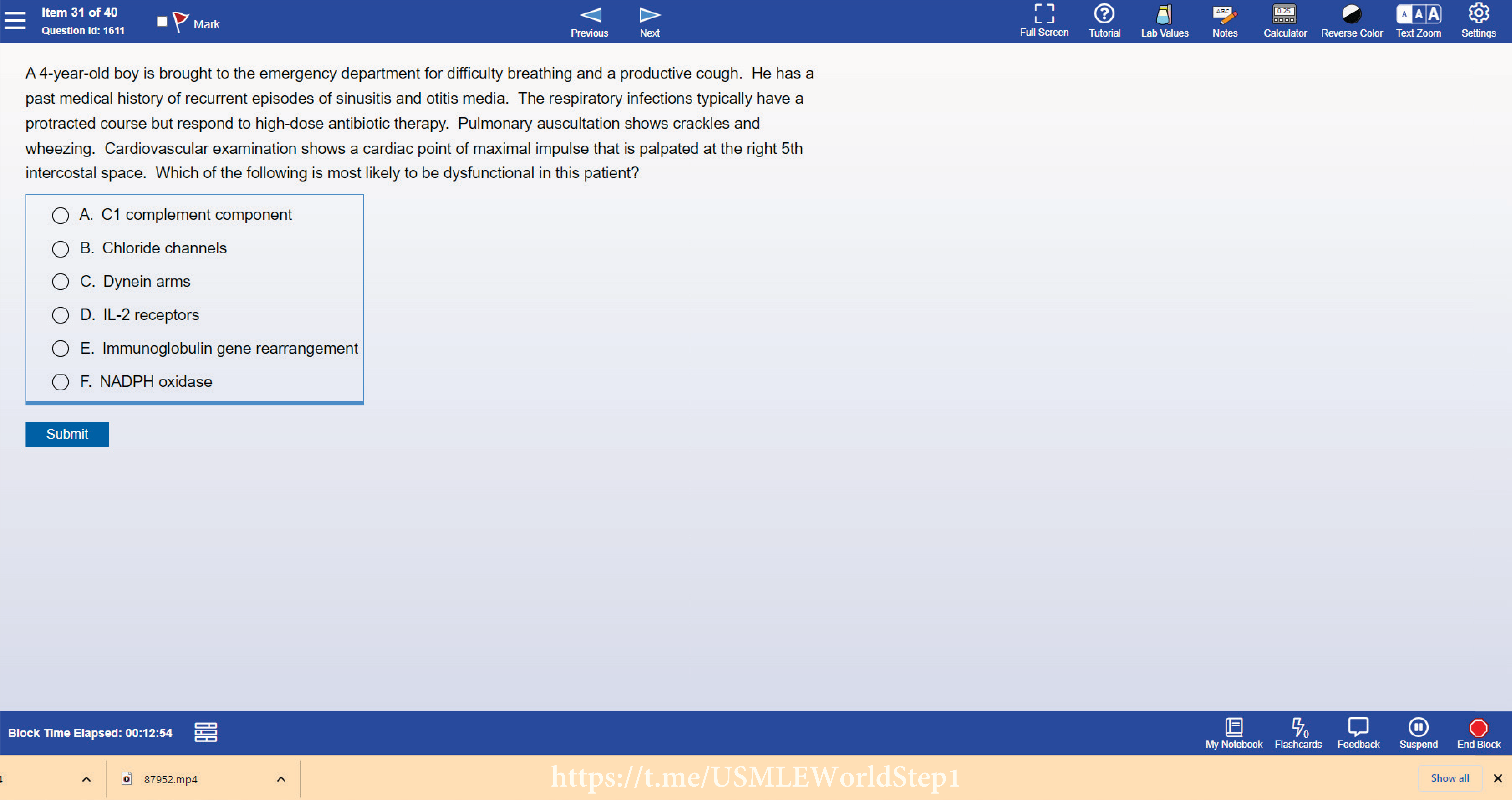
©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Copyright © UWorld. All rights reserved.

Block Time Elapsed: 00:12:53

My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Item 31 of 40
Question Id: 1611

A 4-year-old boy is brought to the emergency department for difficulty breathing and a productive cough. He has a past medical history of recurrent episodes of sinusitis and otitis media. The respiratory infections typically have a protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th intercostal space. Which of the following is most likely to be dysfunctional in this patient?

○ A. C1 complement component
○ B. Chloride channels
○ C. Dynein arms
○ D. IL-2 receptors
○ E. Immunoglobulin gene rearrangement
○ F. NADPH oxidase

Submit

Block Time Elapsed: 00:12:54

A 4-year-old boy is brought to the emergency department for difficulty breathing and a productive cough. He has a past medical history of recurrent episodes of sinusitis and otitis media. The respiratory infections typically have a protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th intercostal space. Which of the following is most likely to be dysfunctional in this patient?

- ○ A. C1 complement component (2%)
- ○ B. Chloride channels (10%)
- ✓ ● C. Dynein arms (72%)
- ○ D. IL-2 receptors (2%)
- ○ E. Immunoglobulin gene rearrangement (4%)
- ○ F. NADPH oxidase (7%)

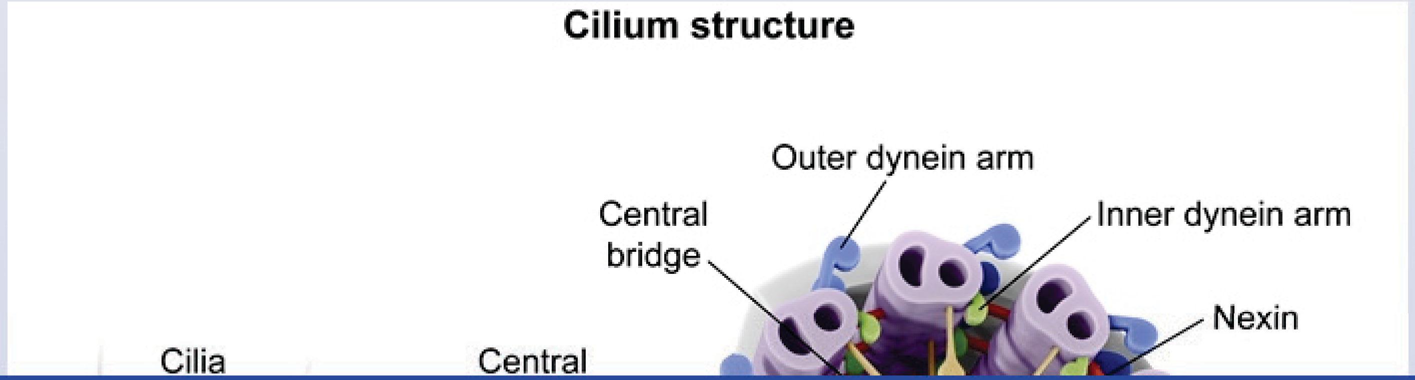
Correct

72% Answered correctly

04 secs Time Spent

2023 Version

Explanation


Cilium structure

87952.mp4
Show all

protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th interco

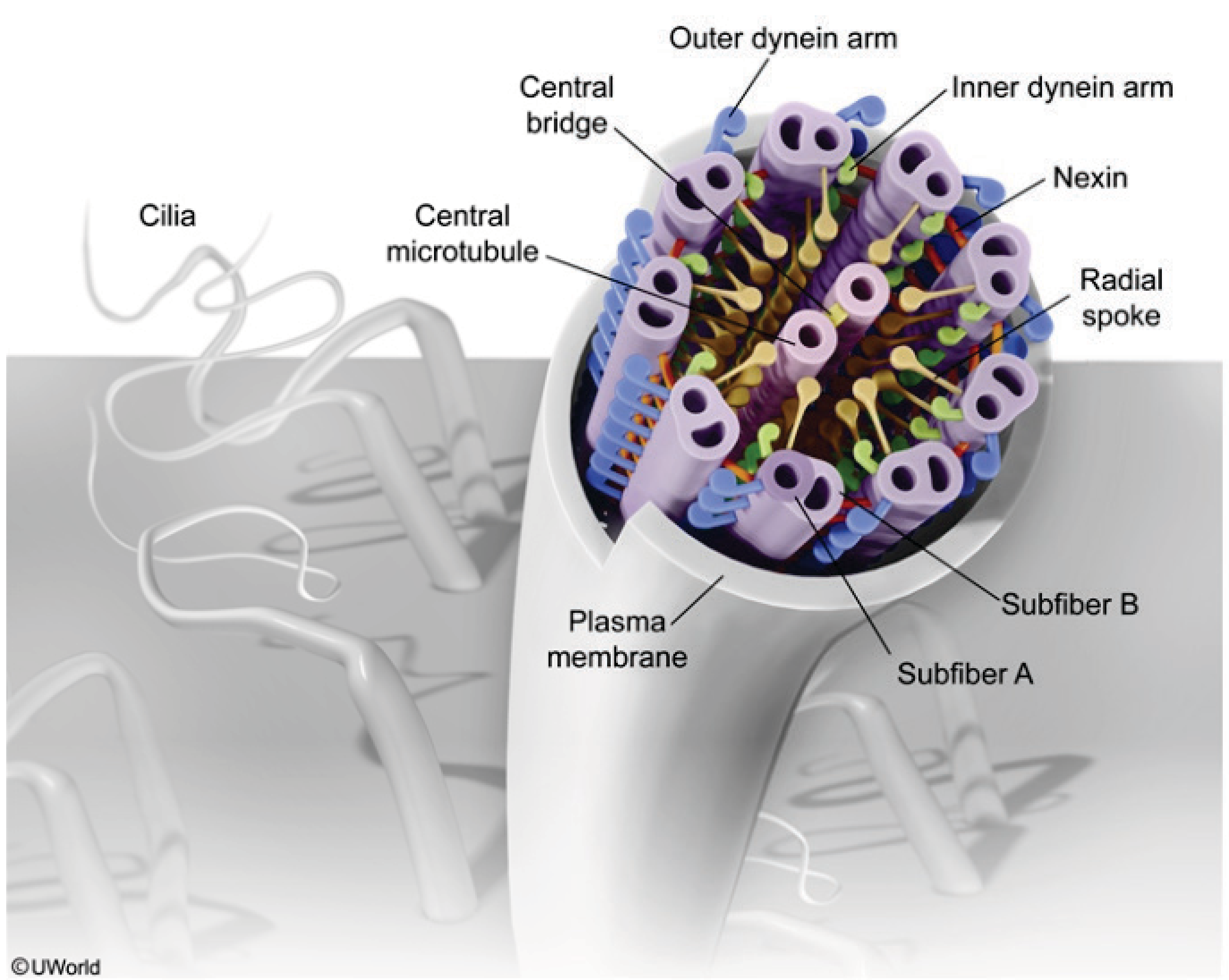
○
○
✓ ●
○
○
○

Cor

Expl

Exhibit Display

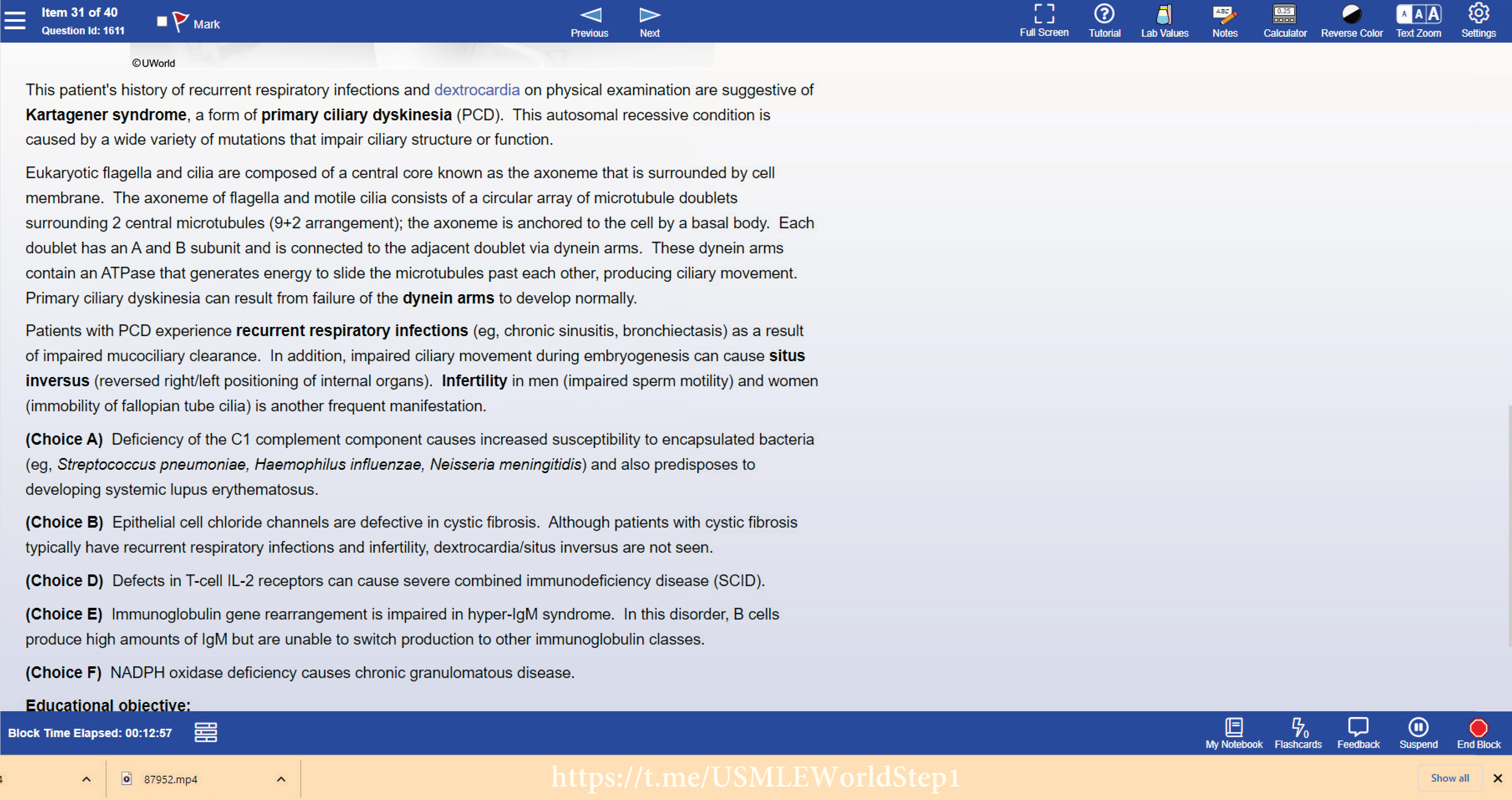
Cilium structure


Outer dynein arm
Central bridge
Inner dynein arm
Nexin
Cilia
Central microtubule
Radial spoke
Plasma membrane
Subfiber B
Subfiber A

©UWorld

Zoom In
Zoom Out
Reset
New |
Existing
My Notebook

87952.mp4
Show all



©UWorld

This patient's history of recurrent respiratory infections and dextrocardia on physical examination are suggestive of **Kartagener syndrome**, a form of **primary ciliary dyskinesia** (PCD). This autosomal recessive condition is caused by a wide variety of mutations that impair ciliary structure or function.

Eukaryotic flagella and cilia are composed of a central core known as the axoneme that is surrounded by cell membrane. The axoneme of flagella and motile cilia consists of a circular array of microtubule doublets surrounding 2 central microtubules (9+2 arrangement); the axoneme is anchored to the cell by a basal body. Each doublet has an A and B subunit and is connected to the adjacent doublet via dynein arms. These dynein arms contain an ATPase that generates energy to slide the microtubules past each other, producing ciliary movement. Primary ciliary dyskinesia can result from failure of the **dynein arms** to develop normally.

Patients with PCD experience **recurrent respiratory infections** (eg, chronic sinusitis, bronchiectasis) as a result of impaired mucociliary clearance. In addition, impaired ciliary movement during embryogenesis can cause **situs inversus** (reversed right/left positioning of internal organs). **Infertility** in men (impaired sperm motility) and women (immobility of fallopian tube cilia) is another frequent manifestation.

(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated bacteria (eg, *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) and also predisposes to developing systemic lupus erythematosus.

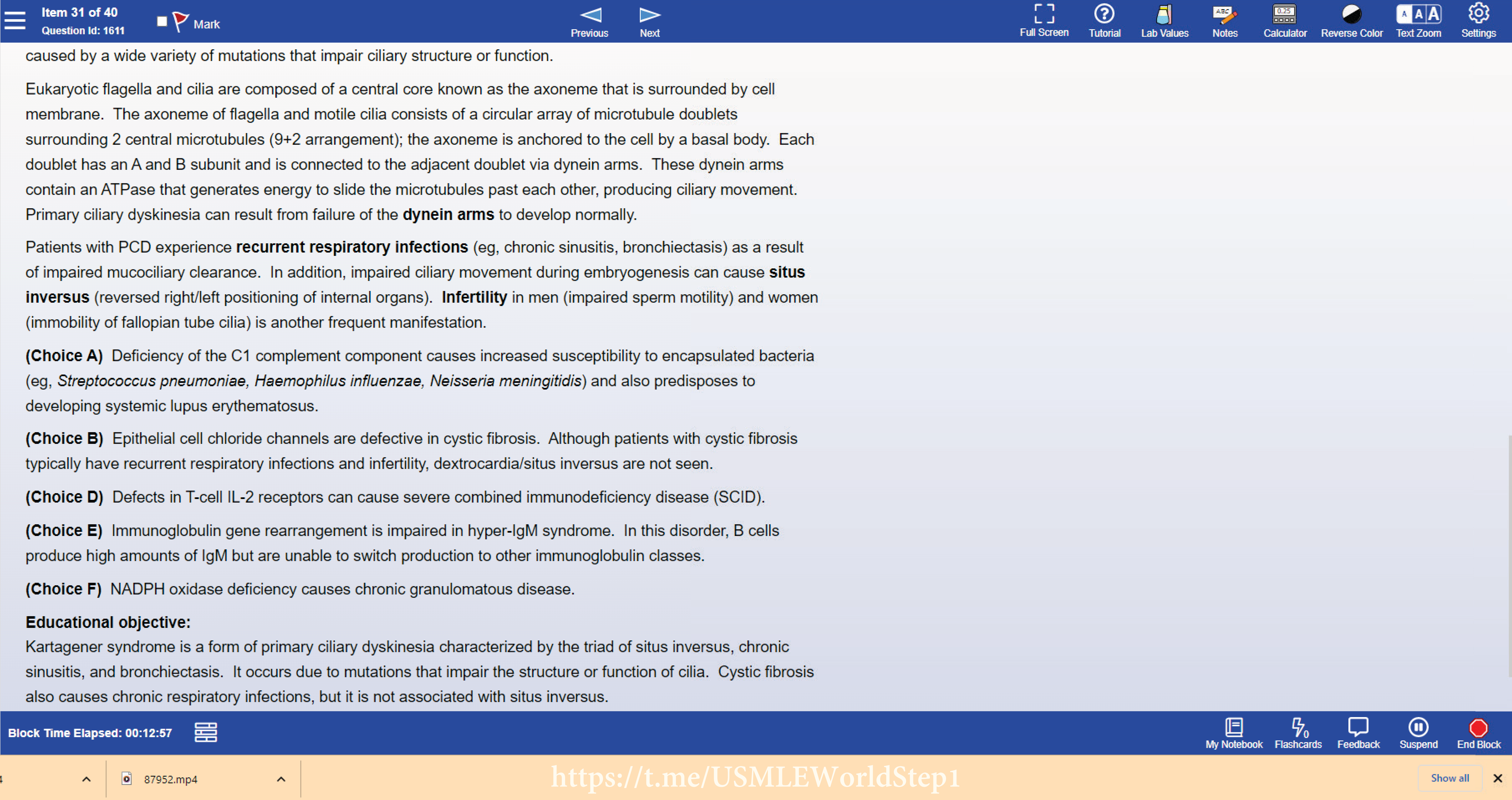
(Choice B) Epithelial cell chloride channels are defective in cystic fibrosis. Although patients with cystic fibrosis typically have recurrent respiratory infections and infertility, dextrocardia/situs inversus are not seen.

(Choice D) Defects in T-cell IL-2 receptors can cause severe combined immunodeficiency disease (SCID).

(Choice E) Immunoglobulin gene rearrangement is impaired in hyper-IgM syndrome. In this disorder, B cells produce high amounts of IgM but are unable to switch production to other immunoglobulin classes.

(Choice F) NADPH oxidase deficiency causes chronic granulomatous disease.

Educational objective:



caused by a wide variety of mutations that impair ciliary structure or function.

Eukaryotic flagella and cilia are composed of a central core known as the axoneme that is surrounded by cell membrane. The axoneme of flagella and motile cilia consists of a circular array of microtubule doublets surrounding 2 central microtubules (9+2 arrangement); the axoneme is anchored to the cell by a basal body. Each doublet has an A and B subunit and is connected to the adjacent doublet via dynein arms. These dynein arms contain an ATPase that generates energy to slide the microtubules past each other, producing ciliary movement. Primary ciliary dyskinesia can result from failure of the **dynein arms** to develop normally.

Patients with PCD experience **recurrent respiratory infections** (eg, chronic sinusitis, bronchiectasis) as a result of impaired mucociliary clearance. In addition, impaired ciliary movement during embryogenesis can cause **situs inversus** (reversed right/left positioning of internal organs). **Infertility** in men (impaired sperm motility) and women (immobility of fallopian tube cilia) is another frequent manifestation.

(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*) and also predisposes to developing systemic lupus erythematosus.

(Choice B) Epithelial cell chloride channels are defective in cystic fibrosis. Although patients with cystic fibrosis typically have recurrent respiratory infections and infertility, dextrocardia/situs inversus are not seen.

(Choice D) Defects in T-cell IL-2 receptors can cause severe combined immunodeficiency disease (SCID).

(Choice E) Immunoglobulin gene rearrangement is impaired in hyper-IgM syndrome. In this disorder, B cells produce high amounts of IgM but are unable to switch production to other immunoglobulin classes.

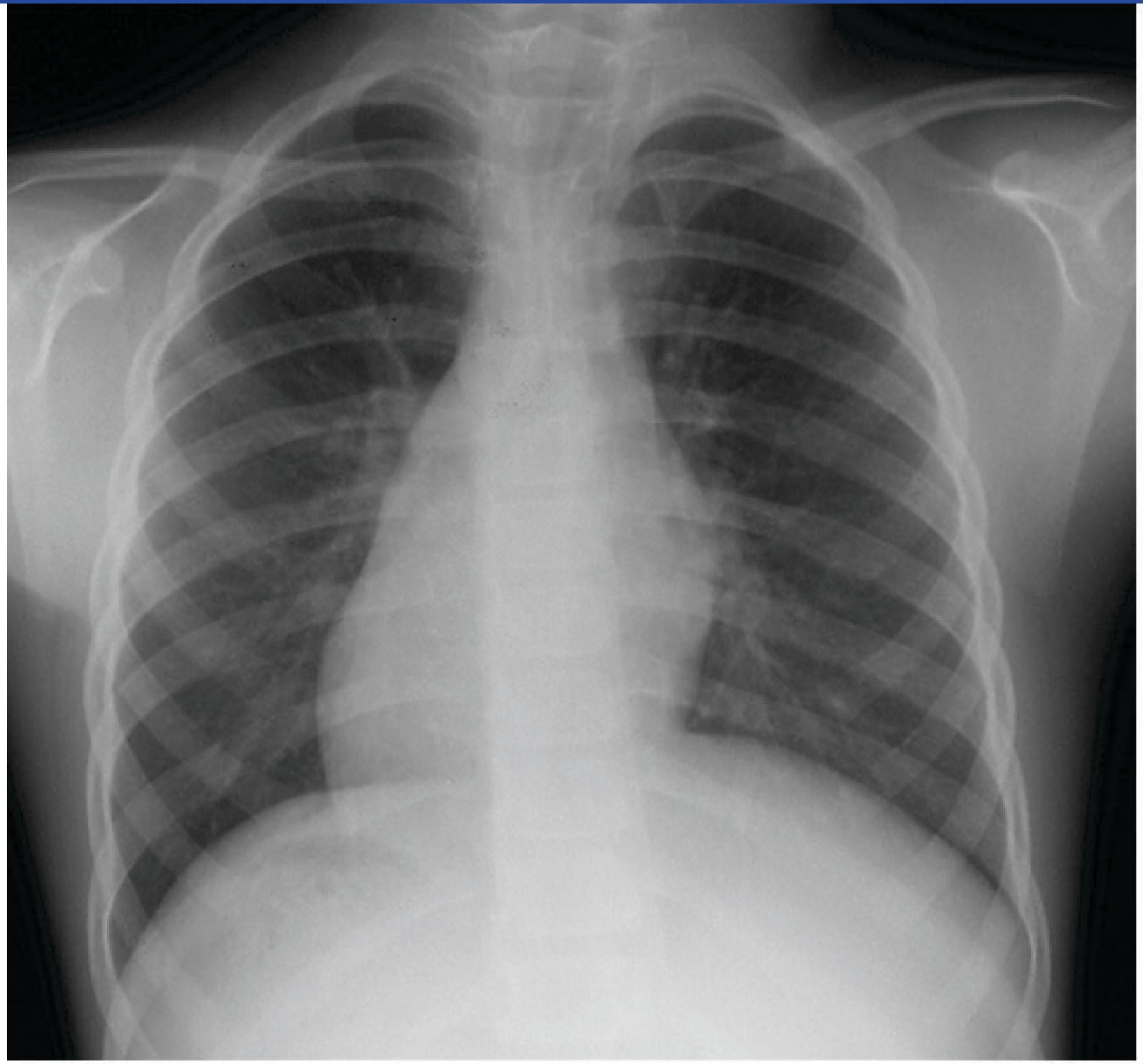
(Choice F) NADPH oxidase deficiency causes chronic granulomatous disease.

Educational objective:

Kartagener syndrome is a form of primary ciliary dyskinesia characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis. It occurs due to mutations that impair the structure or function of cilia. Cystic fibrosis also causes chronic respiratory infections, but it is not associated with situs inversus.

Plasma
Subfiber B

Exhibit Display


Zoom In
Zoom Out
Reset
New
Existing
My Notebook

This p

Kartag

cause

Eukary

memb

surrou

double

contai

Primar

Patien

of imp

invers

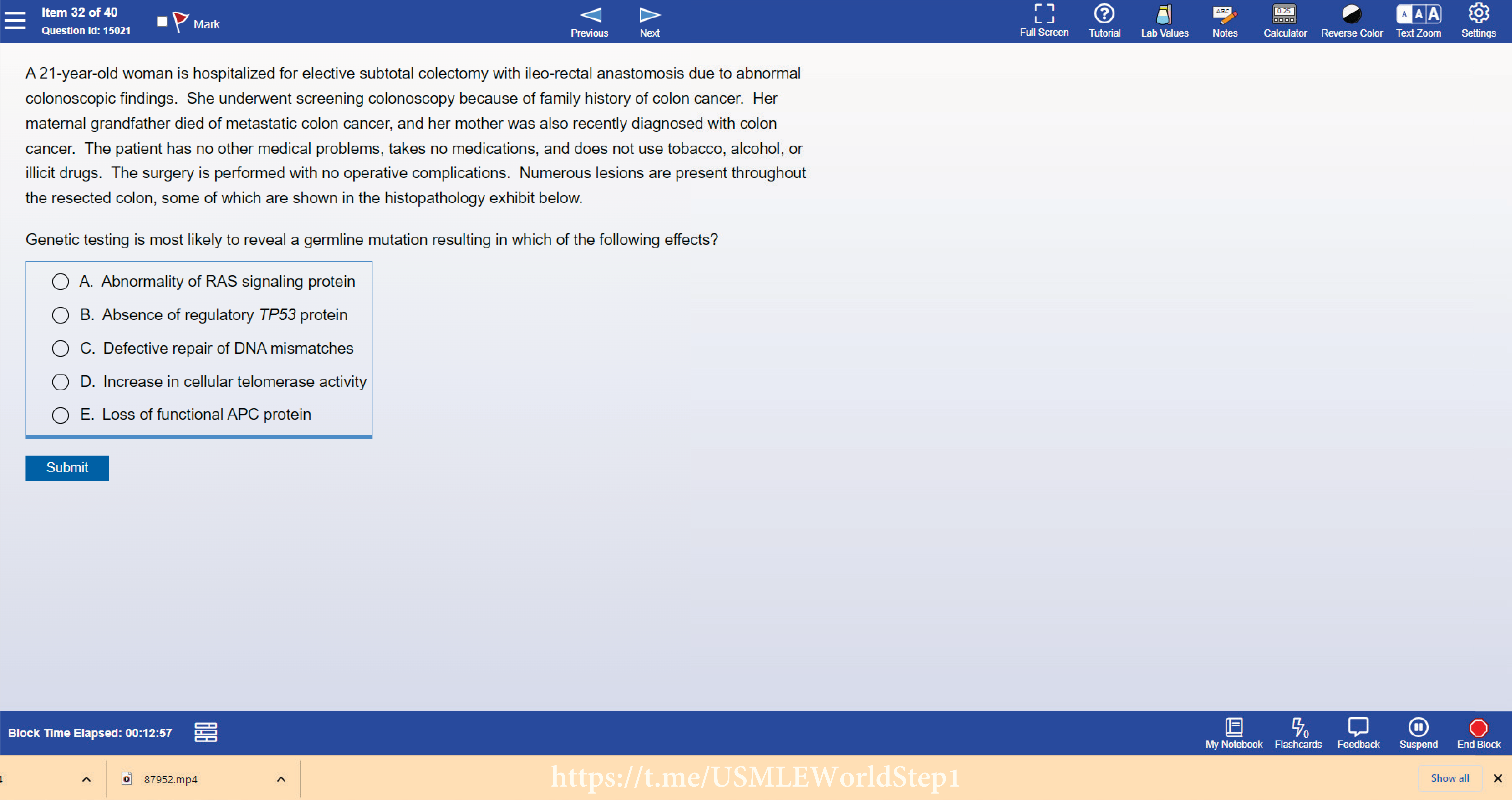
(immo

(Choic

(eg, *S*

develo

(Choice B) Epithelial cell chloride channels are defective in cystic fibrosis. Although patients with cystic fibrosis

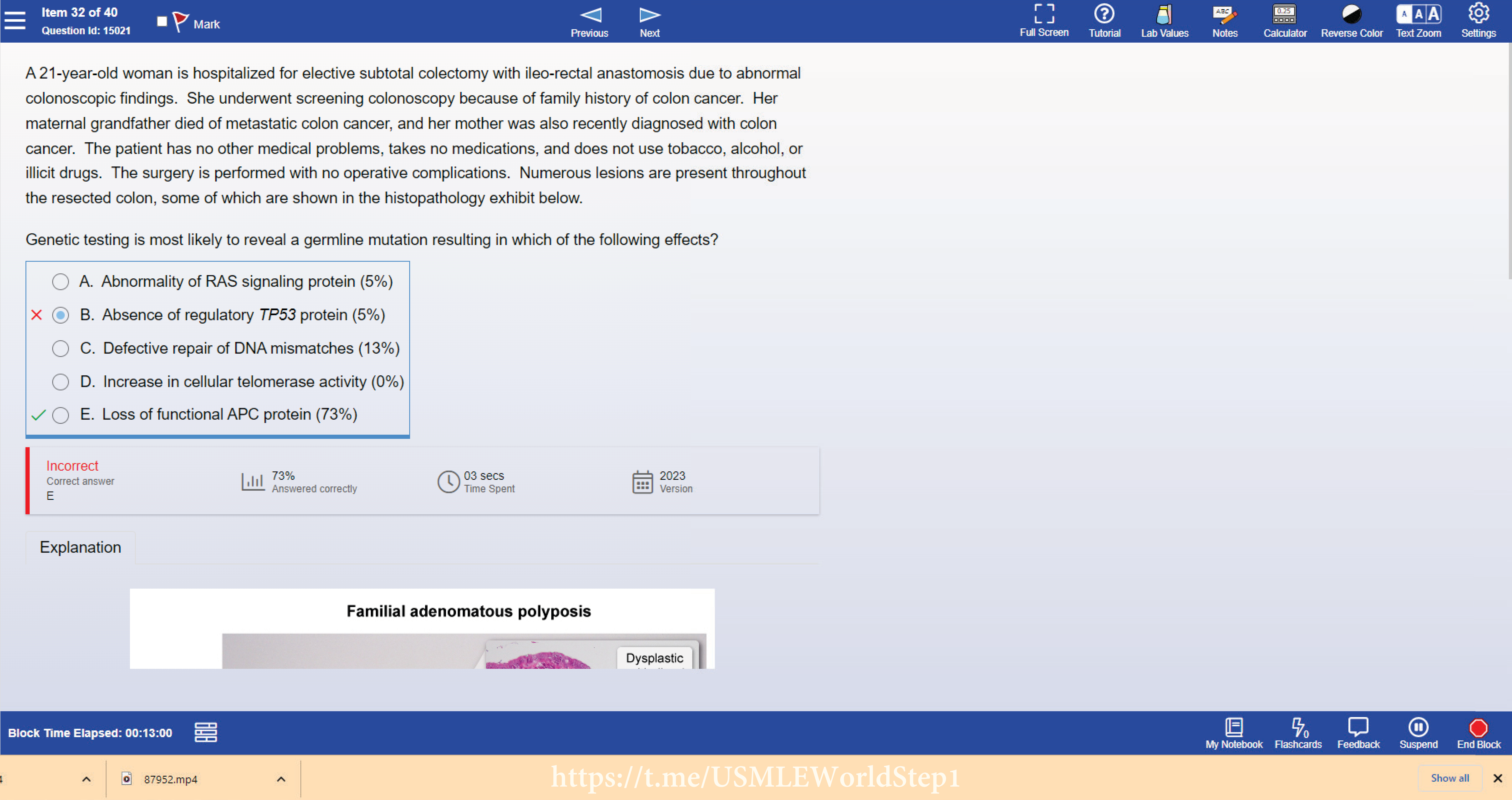

Item 32 of 40
Question Id: 15021
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 21-year-old woman is hospitalized for elective subtotal colectomy with ileo-rectal anastomosis due to abnormal colonoscopic findings. She underwent screening colonoscopy because of family history of colon cancer. Her maternal grandfather died of metastatic colon cancer, and her mother was also recently diagnosed with colon cancer. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. The surgery is performed with no operative complications. Numerous lesions are present throughout the resected colon, some of which are shown in the histopathology exhibit below.

Genetic testing is most likely to reveal a germline mutation resulting in which of the following effects?

○ A. Abnormality of RAS signaling protein
○ B. Absence of regulatory *TP53* protein
○ C. Defective repair of DNA mismatches
○ D. Increase in cellular telomerase activity
○ E. Loss of functional APC protein

Submit
Block Time Elapsed: 00:12:57
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 32 of 40
Question Id: 15021
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 21-year-old woman is hospitalized for elective subtotal colectomy with ileo-rectal anastomosis due to abnormal colonoscopic findings. She underwent screening colonoscopy because of family history of colon cancer. Her maternal grandfather died of metastatic colon cancer, and her mother was also recently diagnosed with colon cancer. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. The surgery is performed with no operative complications. Numerous lesions are present throughout the resected colon, some of which are shown in the histopathology exhibit below.

Genetic testing is most likely to reveal a germline mutation resulting in which of the following effects?

○ A. Abnormality of RAS signaling protein (5%)

✗ ● B. Absence of regulatory *TP53* protein (5%)

○ C. Defective repair of DNA mismatches (13%)

○ D. Increase in cellular telomerase activity (0%)

✓ ○ E. Loss of functional APC protein (73%)

Incorrect
Correct answer
E

73%
Answered correctly

03 secs
Time Spent

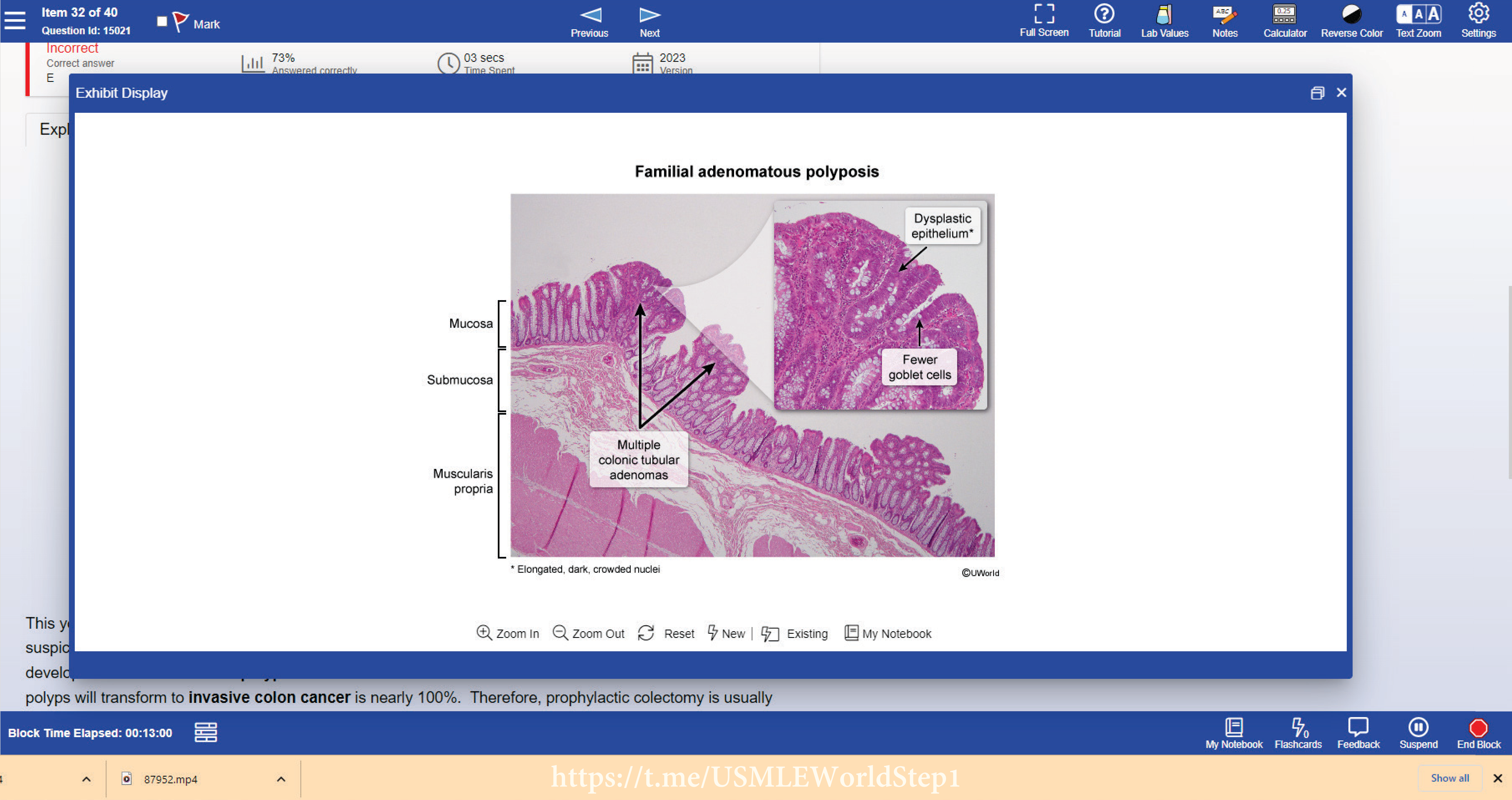
2023
Version

Explanation

Familial adenomatous polyposis

Dysplastic

Block Time Elapsed: 00:13:00
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 32 of 40
Question Id: 15021
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Incorrect
Correct answer
E

73%
Answered correctly

03 secs
Time Spent

2023
Version

Expl

Exhibit Display

Familial adenomatous polyposis

Mucosa
Submucosa
Muscularis propria
Multiple colonic tubular adenomas
Dysplastic epithelium*
Fewer goblet cells

* Elongated, dark, crowded nuclei

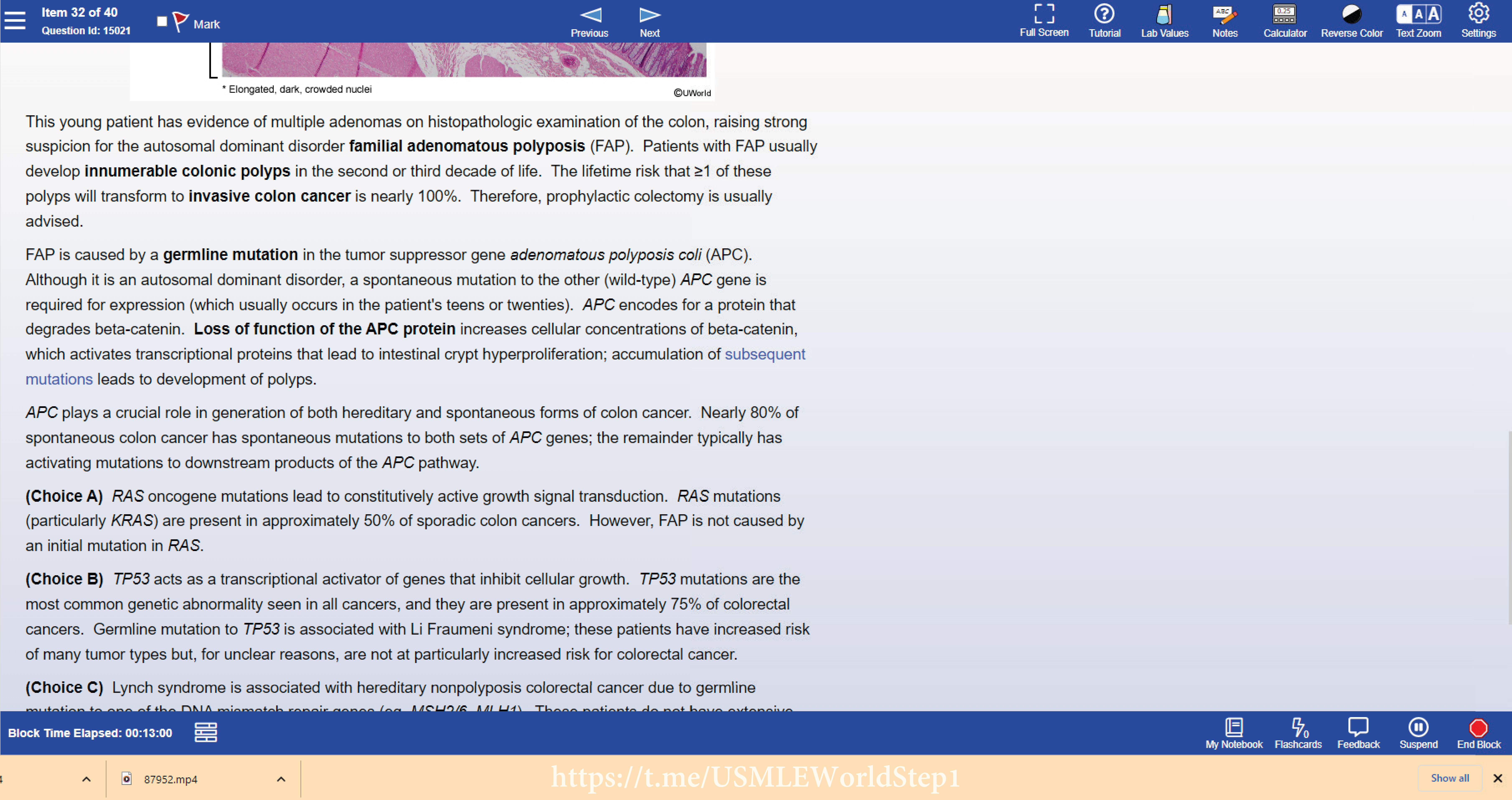
©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

This y
suspic
develo
polyps will transform to **invasive colon cancer** is nearly 100%. Therefore, prophylactic colectomy is usually

Block Time Elapsed: 00:13:00

My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all



* Elongated, dark, crowded nuclei

©UWorld

This young patient has evidence of multiple adenomas on histopathologic examination of the colon, raising strong suspicion for the autosomal dominant disorder **familial adenomatous polyposis** (FAP). Patients with FAP usually develop **innumerable colonic polyps** in the second or third decade of life. The lifetime risk that ≥1 of these polyps will transform to **invasive colon cancer** is nearly 100%. Therefore, prophylactic colectomy is usually advised.

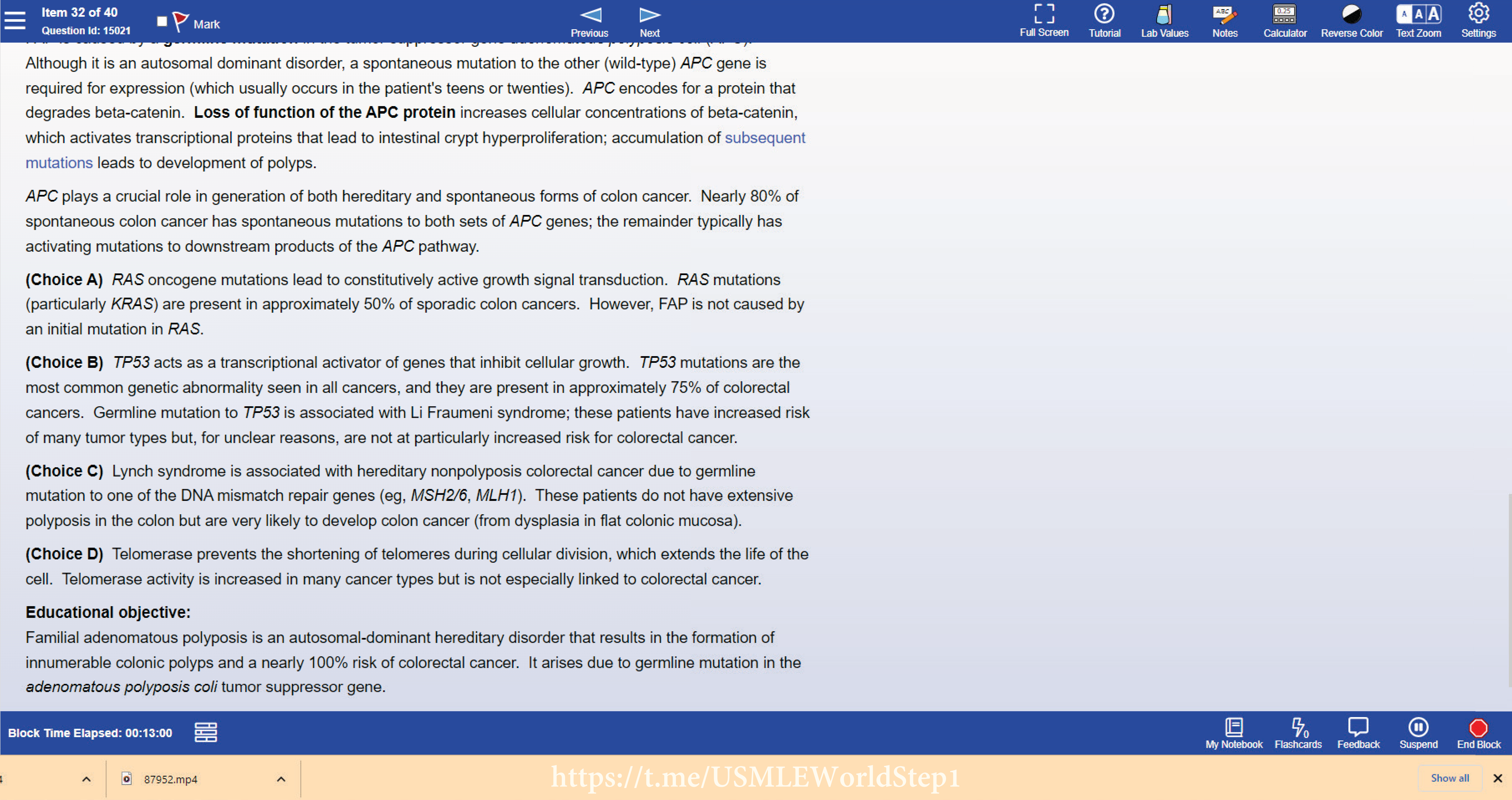
FAP is caused by a **germline mutation** in the tumor suppressor gene *adenomatous polyposis coli* (APC). Although it is an autosomal dominant disorder, a spontaneous mutation to the other (wild-type) *APC* gene is required for expression (which usually occurs in the patient's teens or twenties). *APC* encodes for a protein that degrades beta-catenin. **Loss of function of the APC protein** increases cellular concentrations of beta-catenin, which activates transcriptional proteins that lead to intestinal crypt hyperproliferation; accumulation of subsequent mutations leads to development of polyps.

APC plays a crucial role in generation of both hereditary and spontaneous forms of colon cancer. Nearly 80% of spontaneous colon cancer has spontaneous mutations to both sets of *APC* genes; the remainder typically has activating mutations to downstream products of the *APC* pathway.

(Choice A) *RAS* oncogene mutations lead to constitutively active growth signal transduction. *RAS* mutations (particularly *KRAS*) are present in approximately 50% of sporadic colon cancers. However, FAP is not caused by an initial mutation in *RAS*.

(Choice B) *TP53* acts as a transcriptional activator of genes that inhibit cellular growth. *TP53* mutations are the most common genetic abnormality seen in all cancers, and they are present in approximately 75% of colorectal cancers. Germline mutation to *TP53* is associated with Li Fraumeni syndrome; these patients have increased risk of many tumor types but, for unclear reasons, are not at particularly increased risk for colorectal cancer.

(Choice C) Lynch syndrome is associated with hereditary nonpolyposis colorectal cancer due to germline mutation to one of the DNA mismatch repair genes (eg, *MSH2/6*, *MLH1*). These patients do not have extensive



Although it is an autosomal dominant disorder, a spontaneous mutation to the other (wild-type) *APC* gene is required for expression (which usually occurs in the patient's teens or twenties). *APC* encodes for a protein that degrades beta-catenin. **Loss of function of the APC protein** increases cellular concentrations of beta-catenin, which activates transcriptional proteins that lead to intestinal crypt hyperproliferation; accumulation of subsequent mutations leads to development of polyps.

APC plays a crucial role in generation of both hereditary and spontaneous forms of colon cancer. Nearly 80% of spontaneous colon cancer has spontaneous mutations to both sets of *APC* genes; the remainder typically has activating mutations to downstream products of the *APC* pathway.

(Choice A) *RAS* oncogene mutations lead to constitutively active growth signal transduction. *RAS* mutations (particularly *KRAS*) are present in approximately 50% of sporadic colon cancers. However, FAP is not caused by an initial mutation in *RAS*.

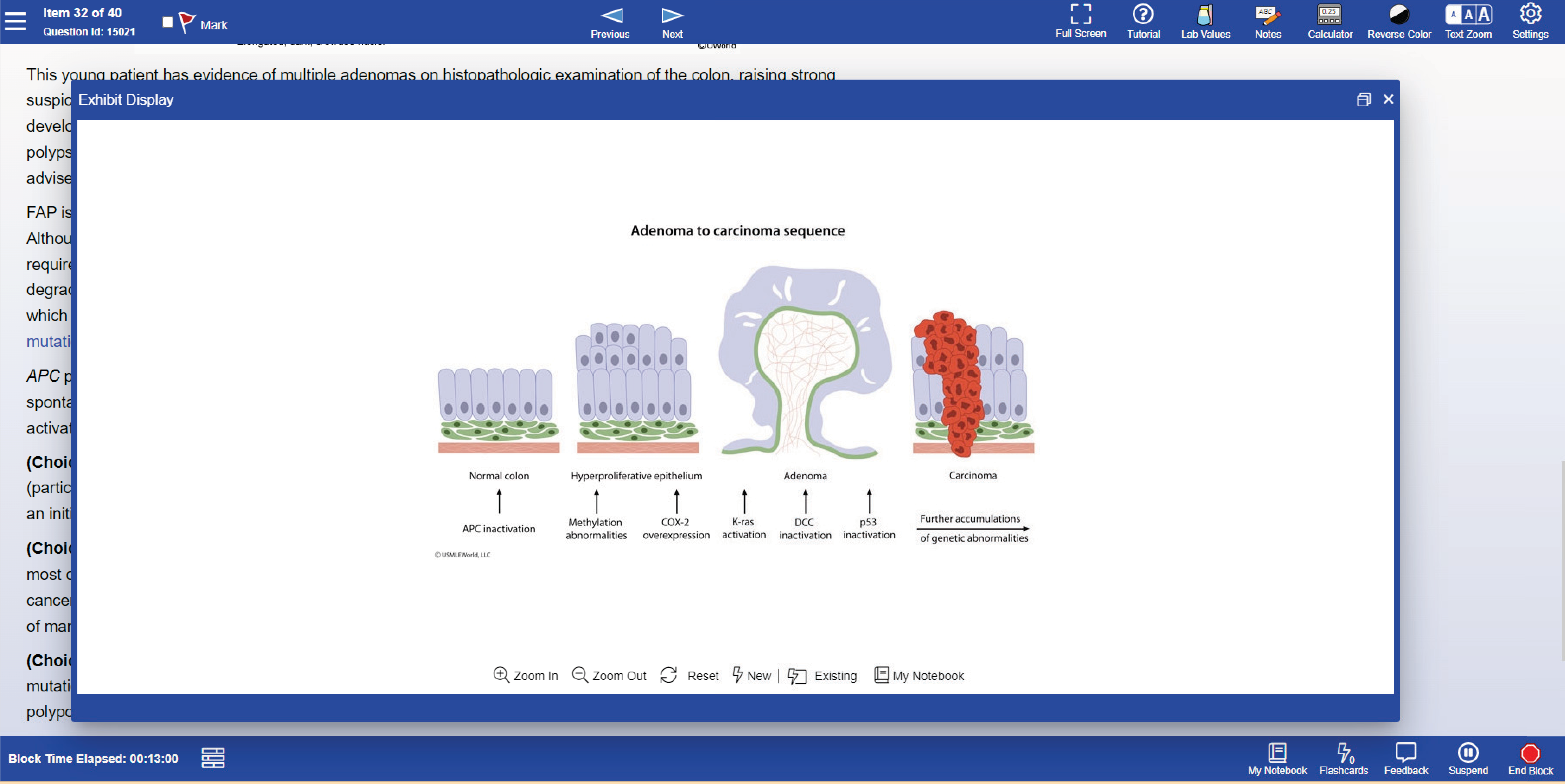
(Choice B) *TP53* acts as a transcriptional activator of genes that inhibit cellular growth. *TP53* mutations are the most common genetic abnormality seen in all cancers, and they are present in approximately 75% of colorectal cancers. Germline mutation to *TP53* is associated with Li Fraumeni syndrome; these patients have increased risk of many tumor types but, for unclear reasons, are not at particularly increased risk for colorectal cancer.

(Choice C) Lynch syndrome is associated with hereditary nonpolyposis colorectal cancer due to germline mutation to one of the DNA mismatch repair genes (eg, *MSH2/6*, *MLH1*). These patients do not have extensive polyposis in the colon but are very likely to develop colon cancer (from dysplasia in flat colonic mucosa).

(Choice D) Telomerase prevents the shortening of telomeres during cellular division, which extends the life of the cell. Telomerase activity is increased in many cancer types but is not especially linked to colorectal cancer.

Educational objective:

Familial adenomatous polyposis is an autosomal-dominant hereditary disorder that results in the formation of innumerable colonic polyps and a nearly 100% risk of colorectal cancer. It arises due to germline mutation in the *adenomatous polyposis coli* tumor suppressor gene.


Item 32 of 40
Question Id: 15021
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
©UWorld

This young patient has evidence of multiple adenomas on histopathologic examination of the colon, raising strong

suspic

develo

polyps

advise

FAP is

Althou

require

degrad

which

mutati

APC p

sponta

activat

(Choi

(partic

an initi

(Choi

most c

cance

of mar

(Choi

mutati

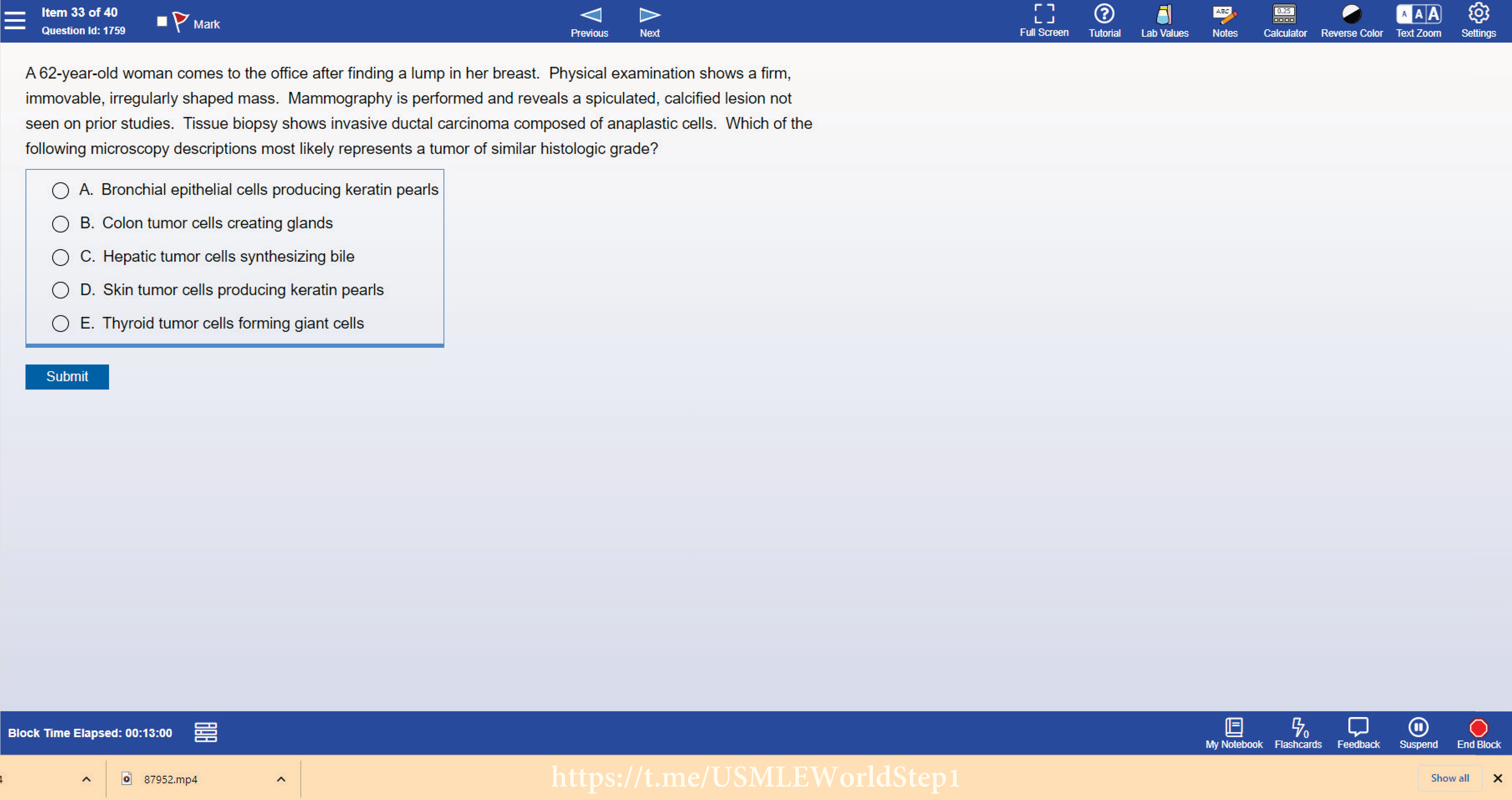
polypo

Exhibit Display
Adenoma to carcinoma sequence
Normal colon
Hyperproliferative epithelium
Adenoma
Carcinoma
APC inactivation
Methylation abnormalities
COX-2 overexpression
K-ras activation
DCC inactivation
p53 inactivation
Further accumulations of genetic abnormalities
© USMLEWorld, LLC
Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:13:00

My Notebook
Flashcards
Feedback
Suspend
End Block

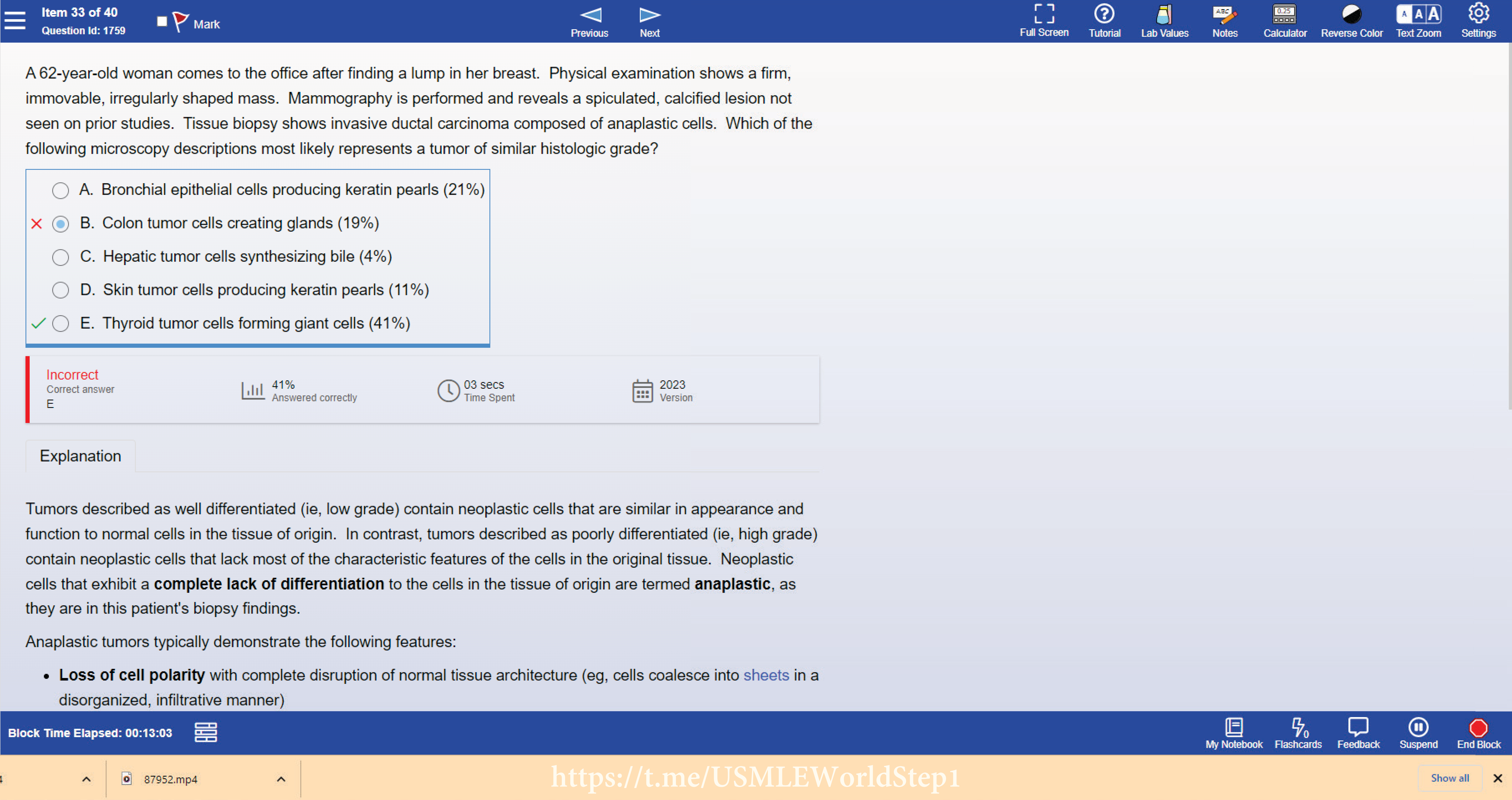
87952.mp4
Show all


Item 33 of 40
Question Id: 1759
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 62-year-old woman comes to the office after finding a lump in her breast. Physical examination shows a firm, immovable, irregularly shaped mass. Mammography is performed and reveals a spiculated, calcified lesion not seen on prior studies. Tissue biopsy shows invasive ductal carcinoma composed of anaplastic cells. Which of the following microscopy descriptions most likely represents a tumor of similar histologic grade?

- ○ A. Bronchial epithelial cells producing keratin pearls
- ○ B. Colon tumor cells creating glands
- ○ C. Hepatic tumor cells synthesizing bile
- ○ D. Skin tumor cells producing keratin pearls
- ○ E. Thyroid tumor cells forming giant cells

Submit
Block Time Elapsed: 00:13:00
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 33 of 40
Question Id: 1759
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 62-year-old woman comes to the office after finding a lump in her breast. Physical examination shows a firm, immovable, irregularly shaped mass. Mammography is performed and reveals a spiculated, calcified lesion not seen on prior studies. Tissue biopsy shows invasive ductal carcinoma composed of anaplastic cells. Which of the following microscopy descriptions most likely represents a tumor of similar histologic grade?

○ A. Bronchial epithelial cells producing keratin pearls (21%)

✗ ● B. Colon tumor cells creating glands (19%)

○ C. Hepatic tumor cells synthesizing bile (4%)

○ D. Skin tumor cells producing keratin pearls (11%)

✓ ○ E. Thyroid tumor cells forming giant cells (41%)

Incorrect
Correct answer
E

41%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

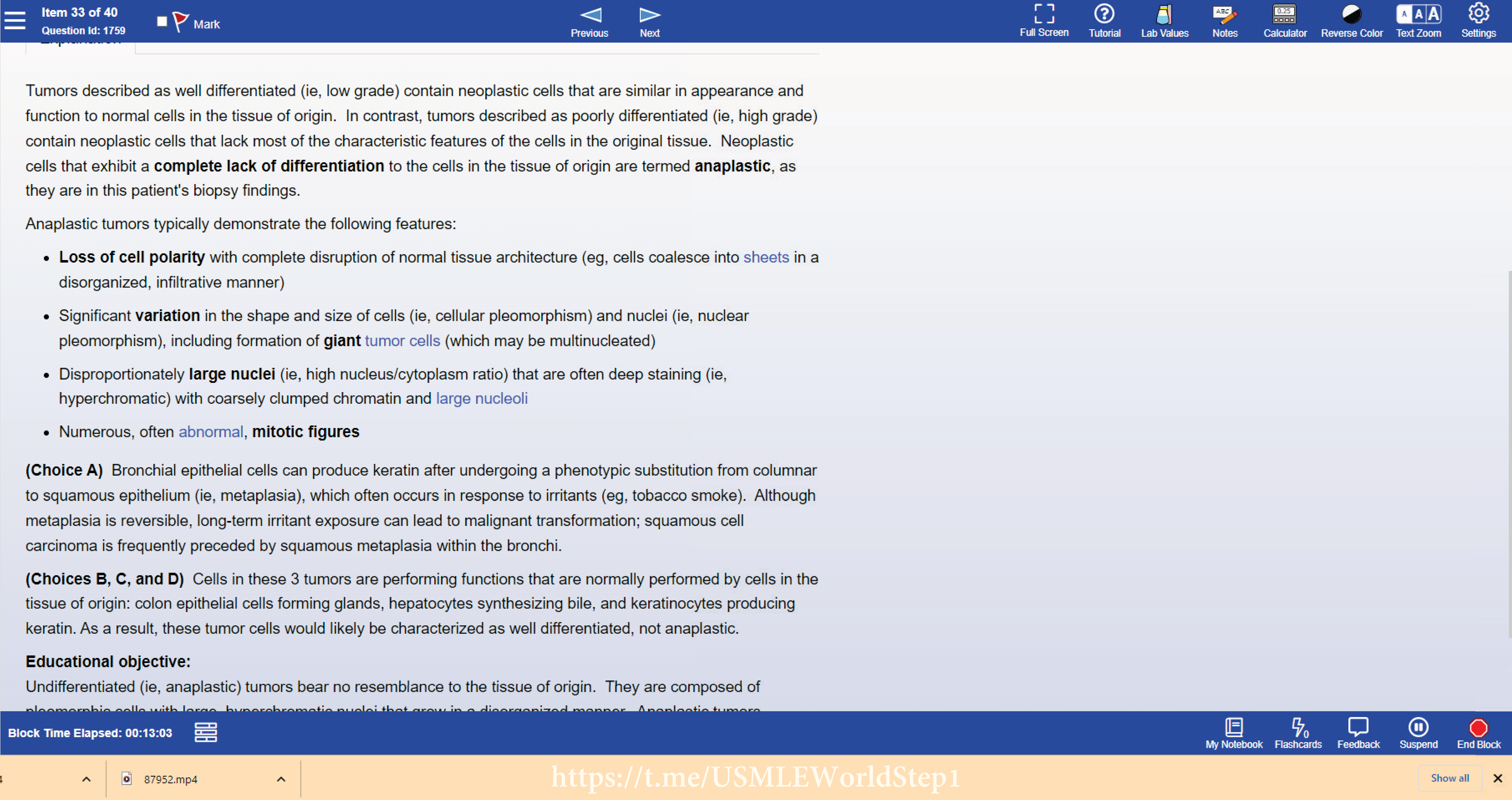
Tumors described as well differentiated (ie, low grade) contain neoplastic cells that are similar in appearance and function to normal cells in the tissue of origin. In contrast, tumors described as poorly differentiated (ie, high grade) contain neoplastic cells that lack most of the characteristic features of the cells in the original tissue. Neoplastic cells that exhibit a **complete lack of differentiation** to the cells in the tissue of origin are termed **anaplastic**, as they are in this patient's biopsy findings.

Anaplastic tumors typically demonstrate the following features:

- **Loss of cell polarity** with complete disruption of normal tissue architecture (eg, cells coalesce into sheets in a disorganized, infiltrative manner)

Block Time Elapsed: 00:13:03

My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all



Tumors described as well differentiated (ie, low grade) contain neoplastic cells that are similar in appearance and function to normal cells in the tissue of origin. In contrast, tumors described as poorly differentiated (ie, high grade) contain neoplastic cells that lack most of the characteristic features of the cells in the original tissue. Neoplastic cells that exhibit a **complete lack of differentiation** to the cells in the tissue of origin are termed **anaplastic**, as they are in this patient's biopsy findings.

Anaplastic tumors typically demonstrate the following features:

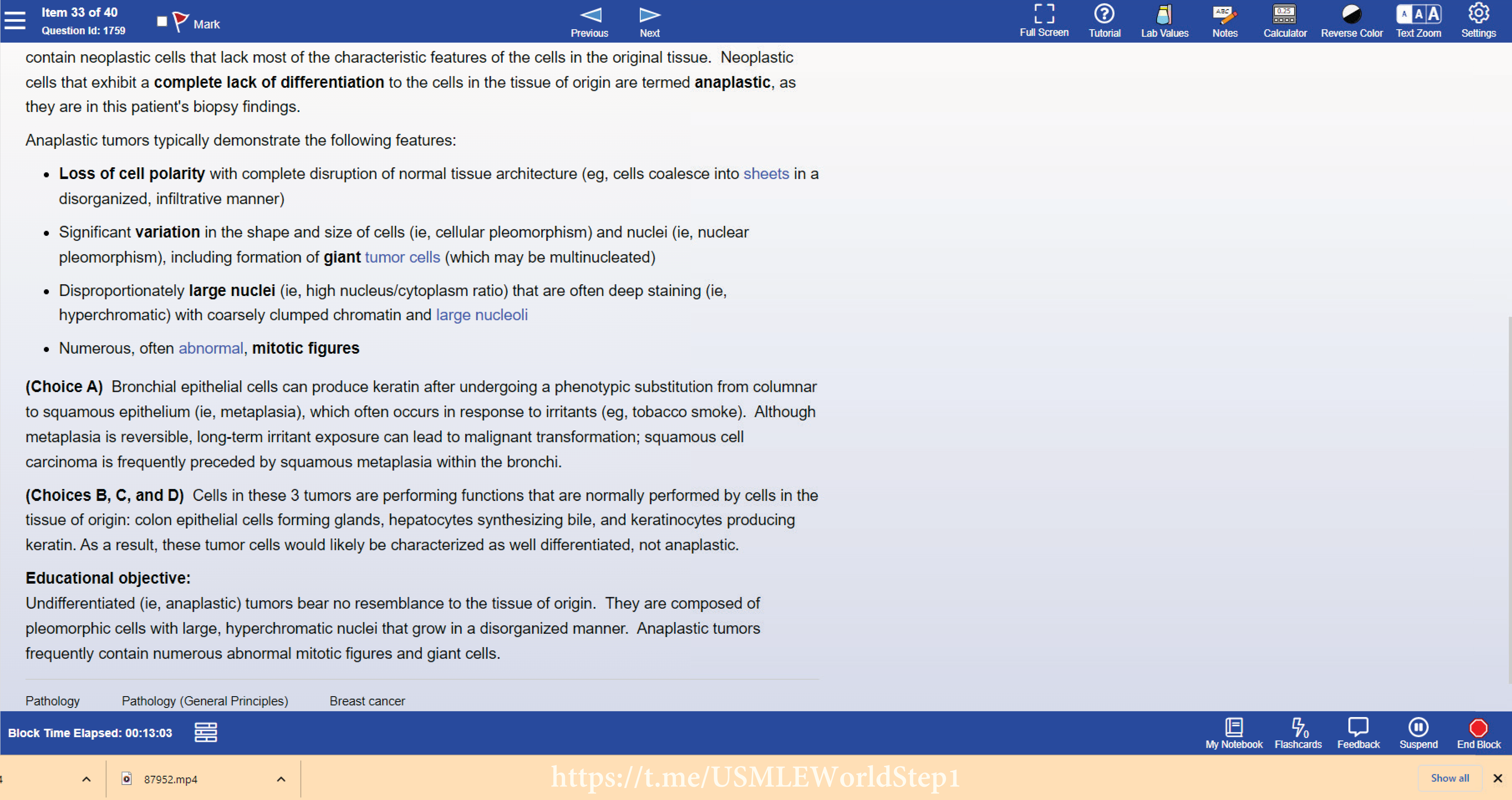
- **Loss of cell polarity** with complete disruption of normal tissue architecture (eg, cells coalesce into sheets in a disorganized, infiltrative manner)
- Significant **variation** in the shape and size of cells (ie, cellular pleomorphism) and nuclei (ie, nuclear pleomorphism), including formation of **giant** tumor cells (which may be multinucleated)
- Disproportionately **large nuclei** (ie, high nucleus/cytoplasm ratio) that are often deep staining (ie, hyperchromatic) with coarsely clumped chromatin and large nucleoli
- Numerous, often abnormal, **mitotic figures**

(Choice A) Bronchial epithelial cells can produce keratin after undergoing a phenotypic substitution from columnar to squamous epithelium (ie, metaplasia), which often occurs in response to irritants (eg, tobacco smoke). Although metaplasia is reversible, long-term irritant exposure can lead to malignant transformation; squamous cell carcinoma is frequently preceded by squamous metaplasia within the bronchi.

(Choices B, C, and D) Cells in these 3 tumors are performing functions that are normally performed by cells in the tissue of origin: colon epithelial cells forming glands, hepatocytes synthesizing bile, and keratinocytes producing keratin. As a result, these tumor cells would likely be characterized as well differentiated, not anaplastic.

Educational objective:

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors


Item 33 of 40
Question Id: 1759
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

contain neoplastic cells that lack most of the characteristic features of the cells in the original tissue. Neoplastic cells that exhibit a **complete lack of differentiation** to the cells in the tissue of origin are termed **anaplastic**, as they are in this patient's biopsy findings.

Anaplastic tumors typically demonstrate the following features:

- **Loss of cell polarity** with complete disruption of normal tissue architecture (eg, cells coalesce into sheets in a disorganized, infiltrative manner)
- Significant **variation** in the shape and size of cells (ie, cellular pleomorphism) and nuclei (ie, nuclear pleomorphism), including formation of **giant** tumor cells (which may be multinucleated)
- Disproportionately **large nuclei** (ie, high nucleus/cytoplasm ratio) that are often deep staining (ie, hyperchromatic) with coarsely clumped chromatin and large nucleoli
- Numerous, often abnormal, **mitotic figures**

(Choice A) Bronchial epithelial cells can produce keratin after undergoing a phenotypic substitution from columnar to squamous epithelium (ie, metaplasia), which often occurs in response to irritants (eg, tobacco smoke). Although metaplasia is reversible, long-term irritant exposure can lead to malignant transformation; squamous cell carcinoma is frequently preceded by squamous metaplasia within the bronchi.

(Choices B, C, and D) Cells in these 3 tumors are performing functions that are normally performed by cells in the tissue of origin: colon epithelial cells forming glands, hepatocytes synthesizing bile, and keratinocytes producing keratin. As a result, these tumor cells would likely be characterized as well differentiated, not anaplastic.

Educational objective:
Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors frequently contain numerous abnormal mitotic figures and giant cells.

Pathology Pathology (General Principles) Breast cancer

Block Time Elapsed: 00:13:03
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Tumor
functio
contai
cells t
they a

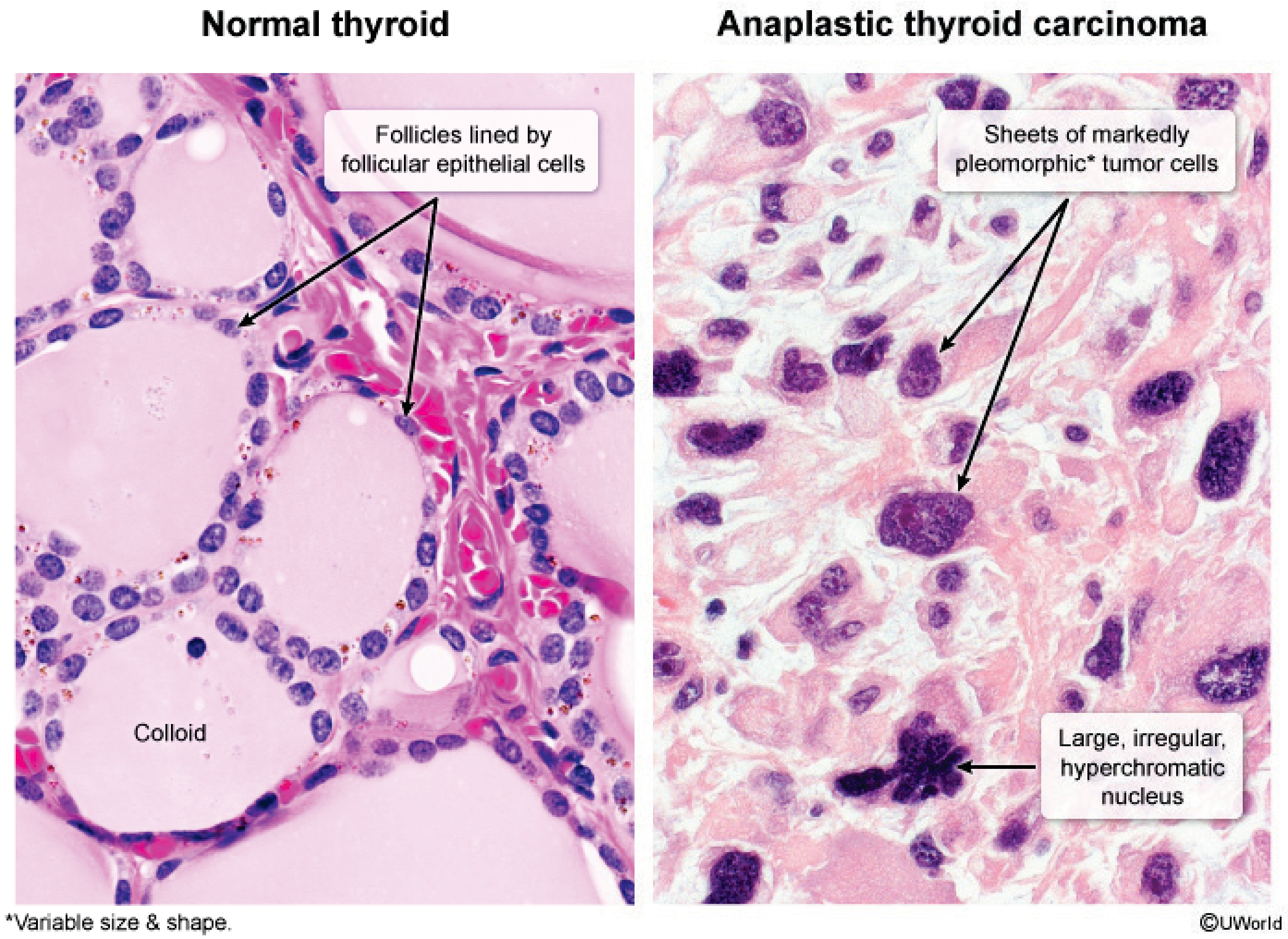
Anapla

- L
  d
- S
  p
- D
  h
- N

(Choi
to squ
metap
carcin

(Choi
tissue
kerati

Exhibit Display



Normal thyroid

Anaplastic thyroid carcinoma

Follicles lined by follicular epithelial cells
Colloid
Sheets of markedly pleomorphic* tumor cells
Large, irregular, hyperchromatic nucleus

*Variable size & shape.

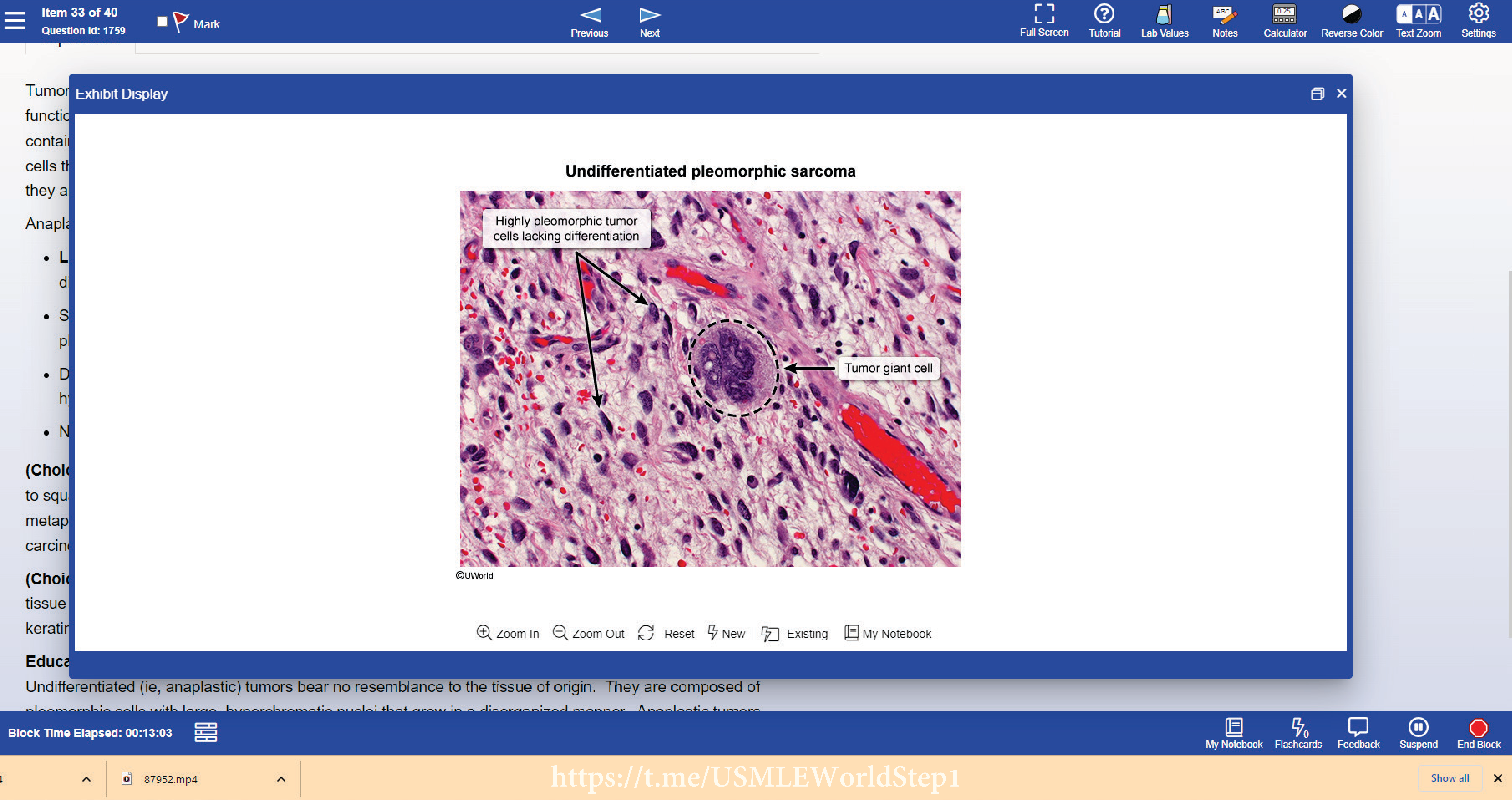
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Educa

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors

87952.mp4
Show all


Item 33 of 40
Question Id: 1759
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:13:03
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Tumor
functic
contai
cells t
they a

Anapl

- L
d
- S
p
- D
h
- N

(Choi
to squ
metap
carcin

(Choi
tissue
keratir

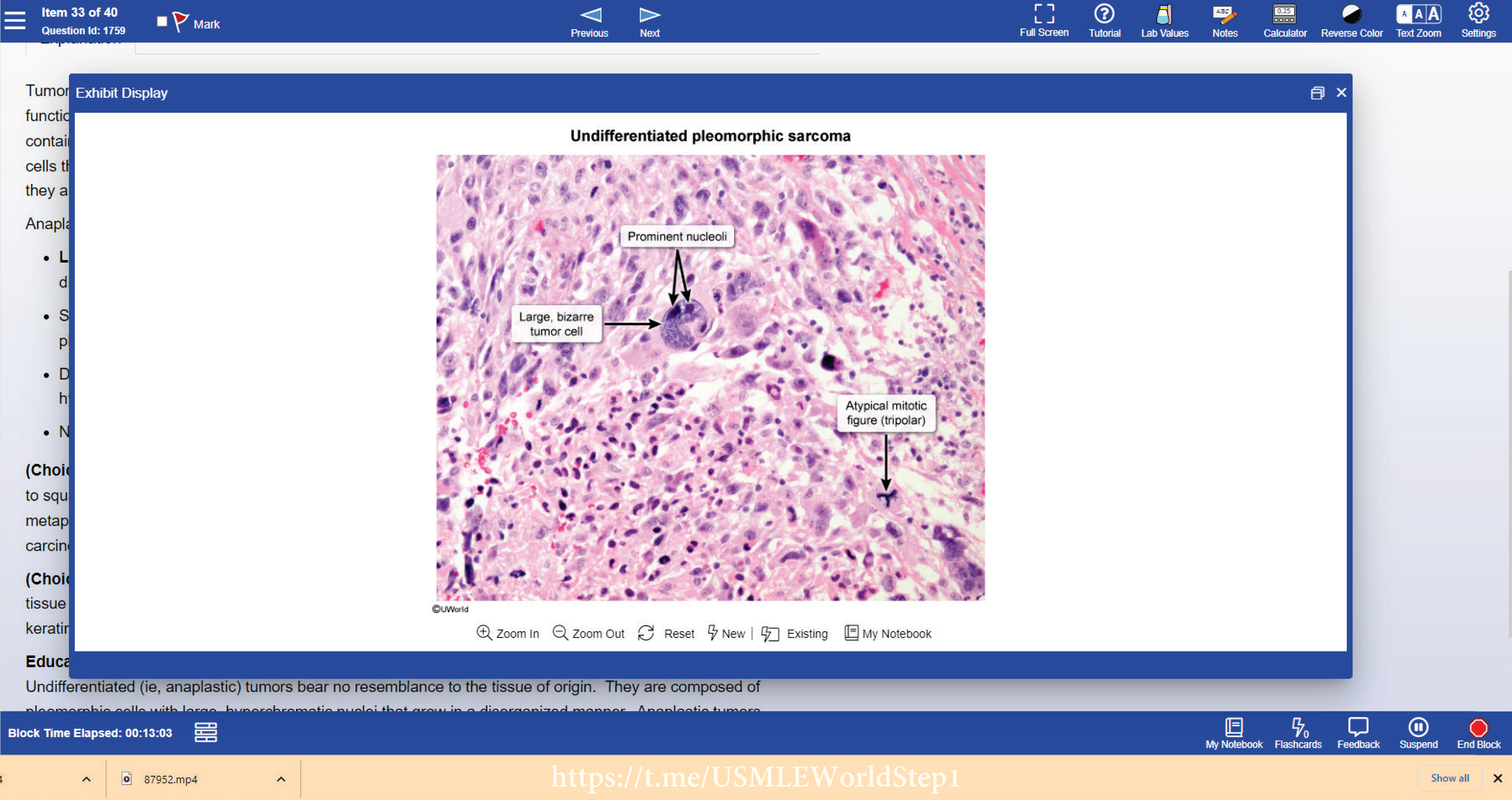
Undifferentiated pleomorphic sarcoma

Highly pleomorphic tumor cells lacking differentiation
Tumor giant cell

©UWorld

Educa

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors


Item 33 of 40
Question Id: 1759
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display

Tumor
functio
contai
cells th
they a

Anapla

- L
  d
- S
  p
- D
  h
- N

(Choi
to squ
metap
carcin

(Choi
tissue
keratin

Educa

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors

Undifferentiated pleomorphic sarcoma

Prominent nucleoli
Large, bizarre tumor cell
Atypical mitotic figure (tripolar)

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:13:03
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Tumor
functio
contai
cells tl
they a

Anapla

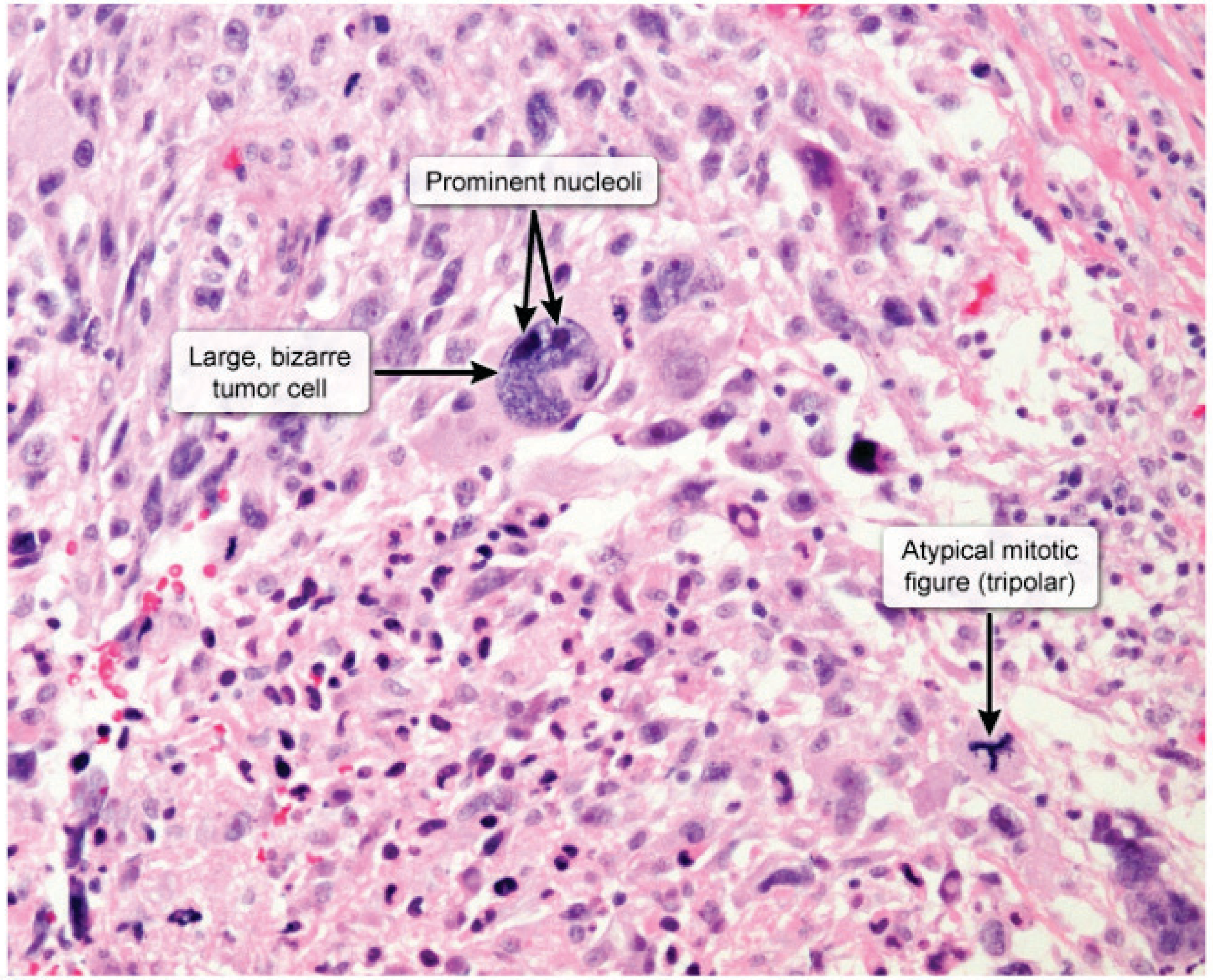
- L
  d
- S
  p
- D
  h
- N

(Choi
to squ
metap
carcin

(Choi
tissue
keratin

Exhibit Display

Undifferentiated pleomorphic sarcoma


Prominent nucleoli
Large, bizarre tumor cell
Atypical mitotic figure (tripolar)

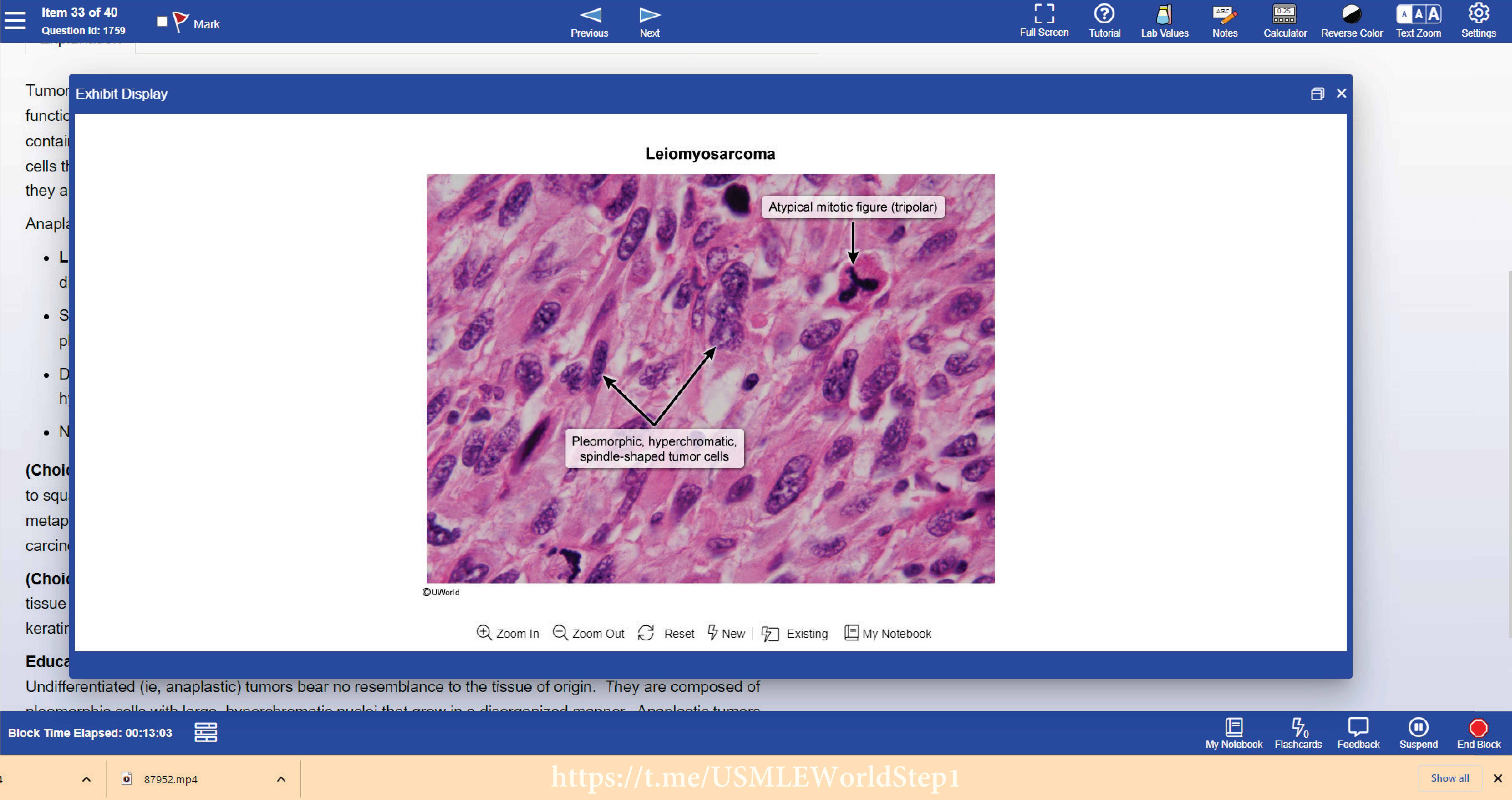
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Educa

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of

87952.mp4
Show all


Item 33 of 40
Question Id: 1759
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:13:03
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Tumor
functic
contai
cells tl
they a

Anapla

- L
  d
- S
  p
- D
  h
- N

(Choi
to squ
metap
carcin

(Choi
tissue
keratir

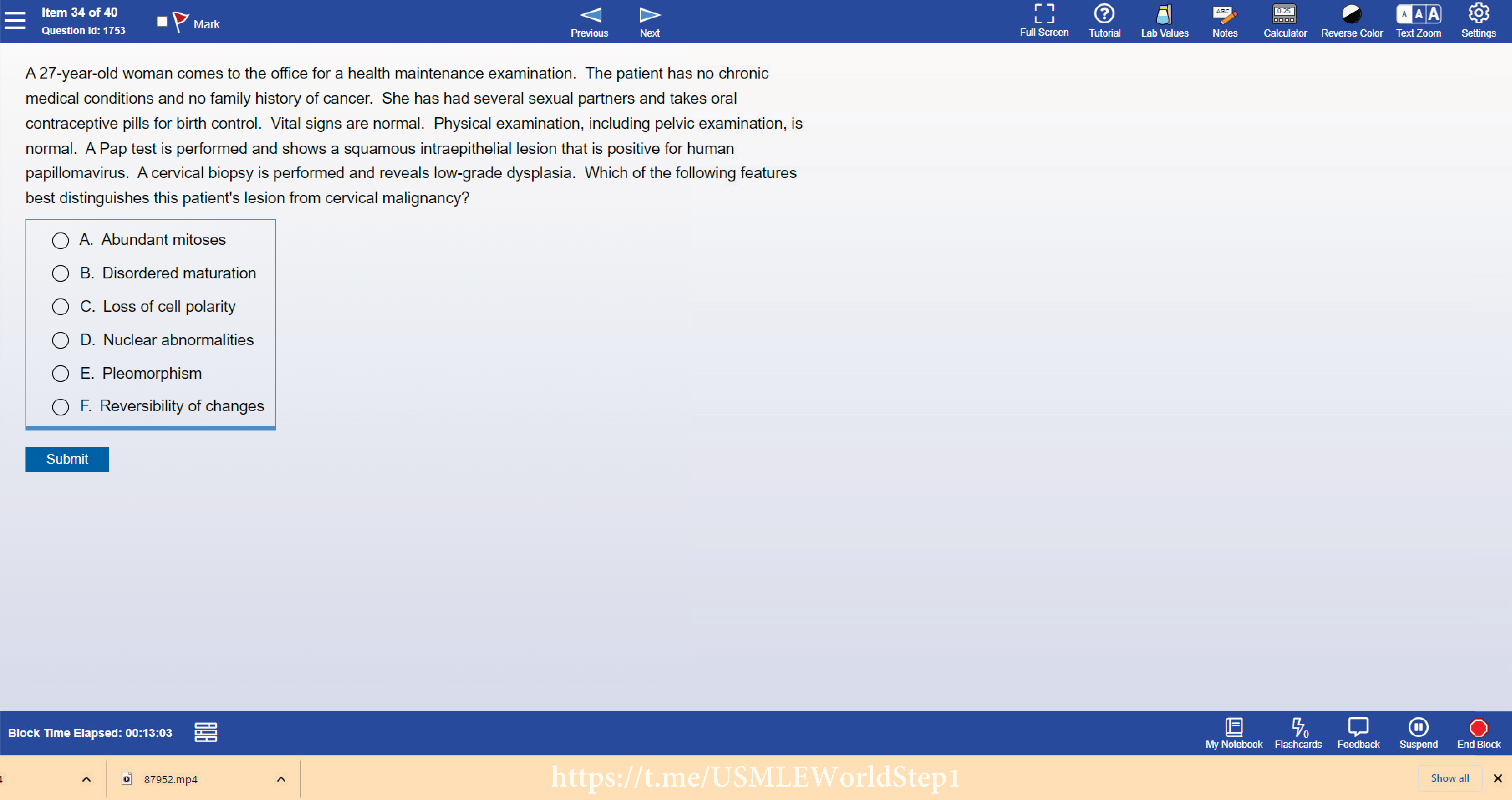
Educa

Undifferentiated (ie, anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized manner. Anaplastic tumors

Leiomyosarcoma

Atypical mitotic figure (tripolar)
Pleomorphic, hyperchromatic, spindle-shaped tumor cells

©UWorld

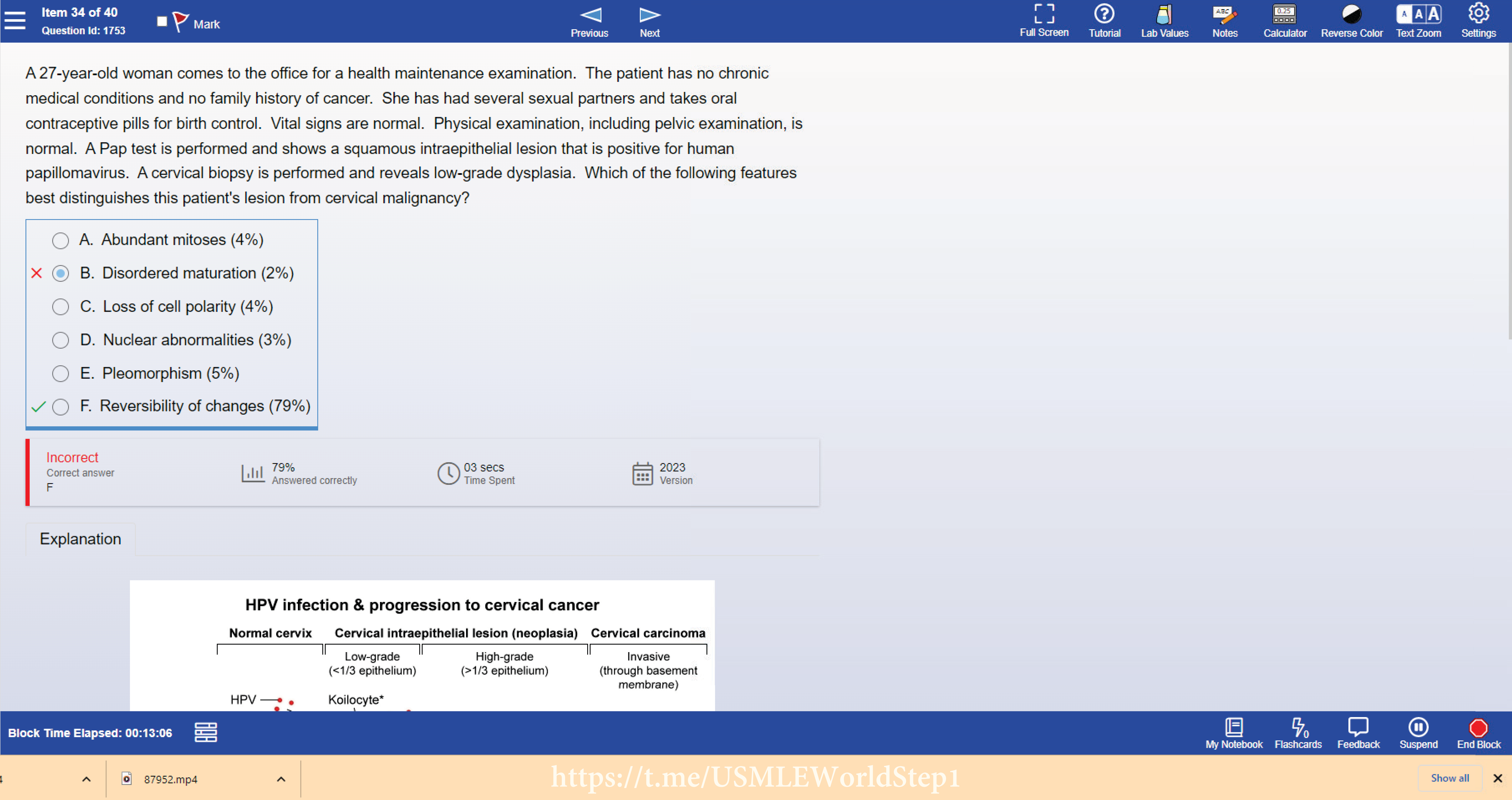

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Item 34 of 40
Question Id: 1753

A 27-year-old woman comes to the office for a health maintenance examination. The patient has no chronic medical conditions and no family history of cancer. She has had several sexual partners and takes oral contraceptive pills for birth control. Vital signs are normal. Physical examination, including pelvic examination, is normal. A Pap test is performed and shows a squamous intraepithelial lesion that is positive for human papillomavirus. A cervical biopsy is performed and reveals low-grade dysplasia. Which of the following features best distinguishes this patient's lesion from cervical malignancy?

- ○ A. Abundant mitoses
- ○ B. Disordered maturation
- ○ C. Loss of cell polarity
- ○ D. Nuclear abnormalities
- ○ E. Pleomorphism
- ○ F. Reversibility of changes

Block Time Elapsed: 00:13:03


Item 34 of 40
Question Id: 1753
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 27-year-old woman comes to the office for a health maintenance examination. The patient has no chronic medical conditions and no family history of cancer. She has had several sexual partners and takes oral contraceptive pills for birth control. Vital signs are normal. Physical examination, including pelvic examination, is normal. A Pap test is performed and shows a squamous intraepithelial lesion that is positive for human papillomavirus. A cervical biopsy is performed and reveals low-grade dysplasia. Which of the following features best distinguishes this patient's lesion from cervical malignancy?

- ○ A. Abundant mitoses (4%)
- ✗ ● B. Disordered maturation (2%)
- ○ C. Loss of cell polarity (4%)
- ○ D. Nuclear abnormalities (3%)
- ○ E. Pleomorphism (5%)
- ✓ ○ F. Reversibility of changes (79%)

Incorrect
Correct answer
F

79%
Answered correctly

03 secs
Time Spent

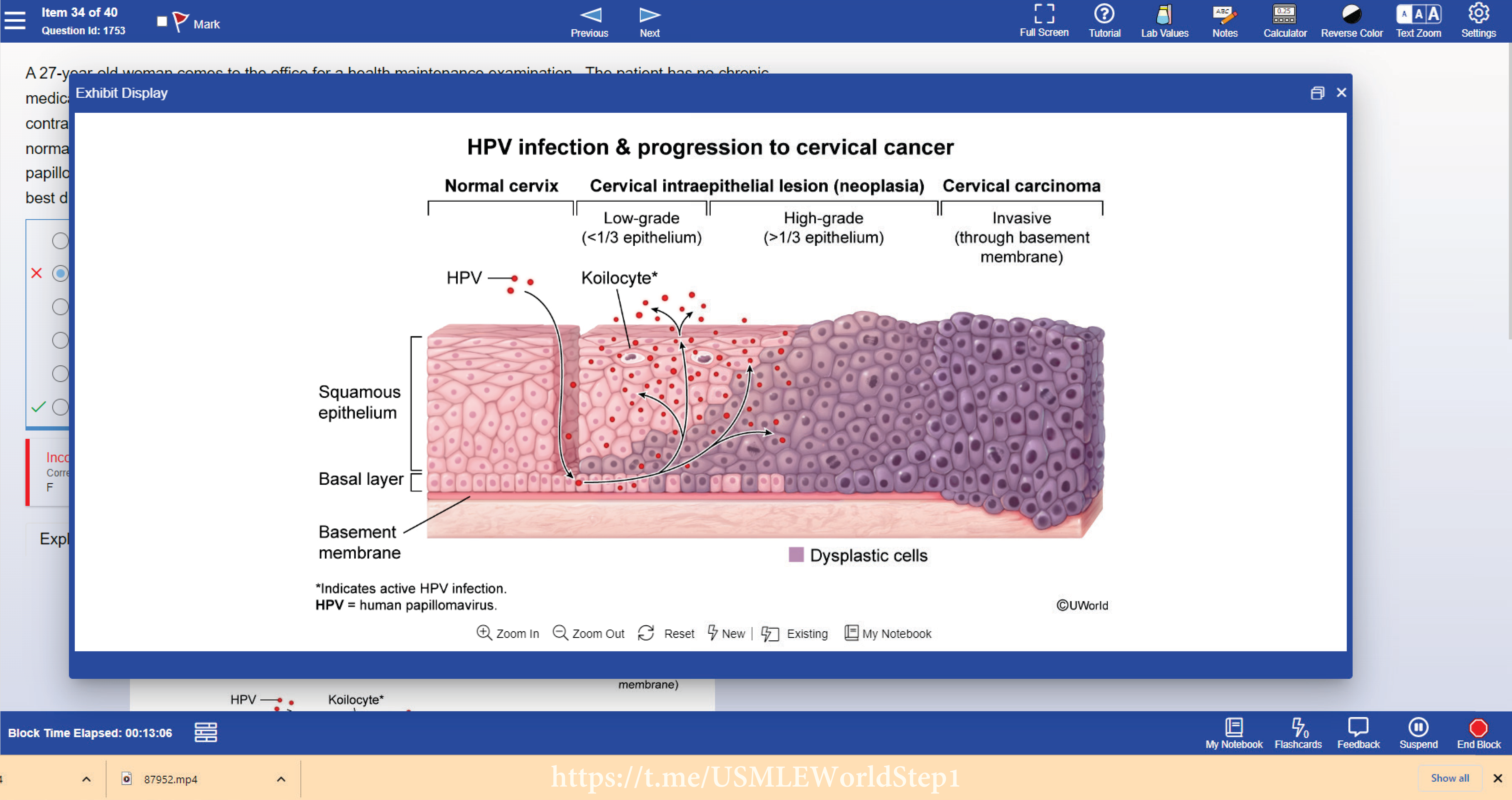
2023
Version

Explanation

HPV infection & progression to cervical cancer

Normal cervix
Cervical intraepithelial lesion (neoplasia)
Cervical carcinoma
Low-grade
(<1/3 epithelium)
High-grade
(>1/3 epithelium)
Invasive
(through basement
membrane)
HPV
Koilocyte*

Block Time Elapsed: 00:13:06
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 34 of 40
Question Id: 1753
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

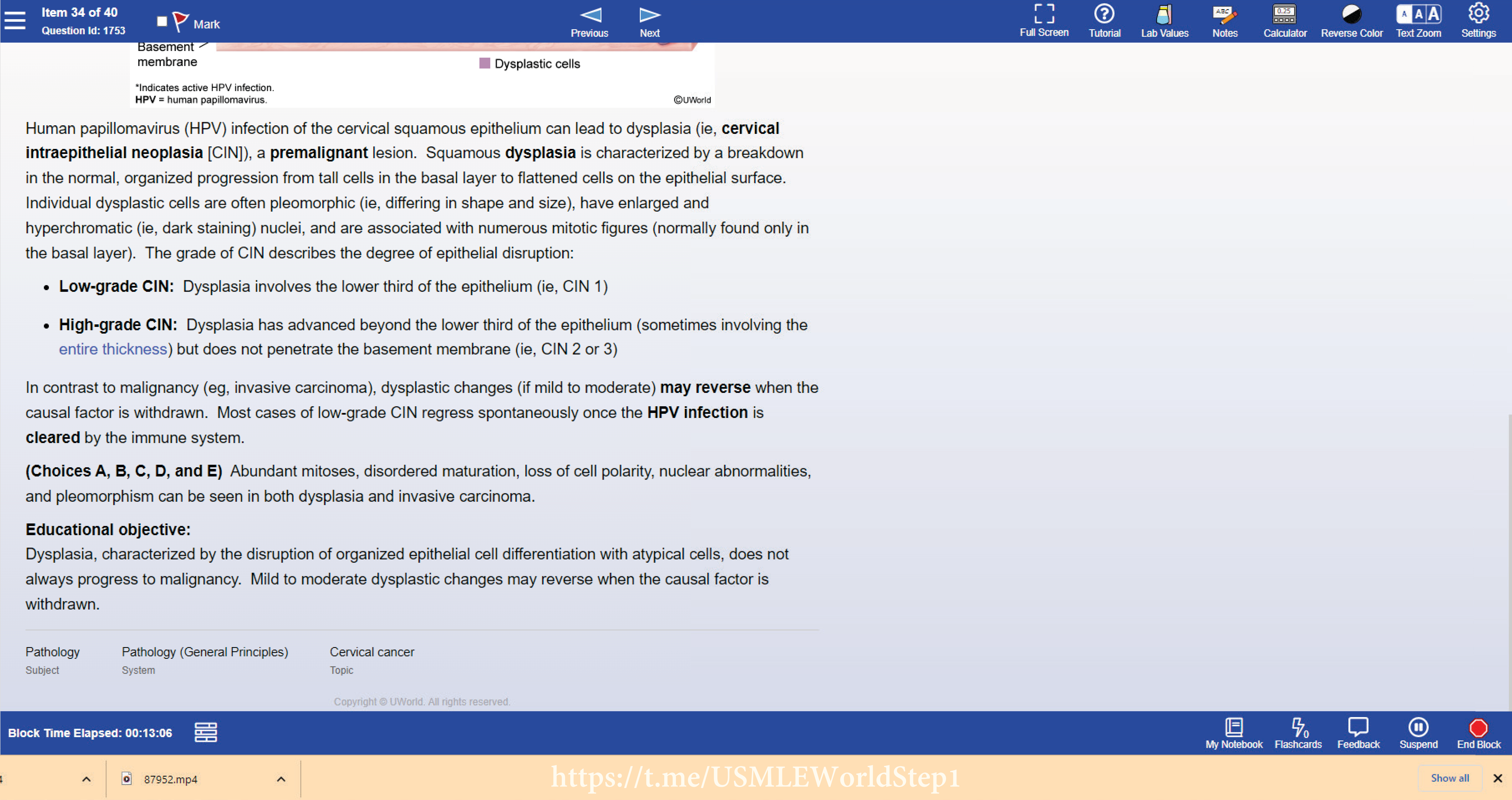
A 27-year-old woman comes to the office for a health maintenance examination. The patient has no chronic
medic
contra
norma
papillo
best d

Inco
Corre
F
Expl
Exhibit Display

HPV infection & progression to cervical cancer

Normal cervix
Cervical intraepithelial lesion (neoplasia)
Cervical carcinoma
Low-grade
(<1/3 epithelium)
High-grade
(>1/3 epithelium)
Invasive
(through basement
membrane)
HPV
Koilocyte*
Squamous
epithelium
Basal layer
Basement
membrane
Dysplastic cells
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
membrane)
HPV
Koilocyte*
Block Time Elapsed: 00:13:06
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

*Indicates active HPV infection.
HPV = human papillomavirus.


Item 34 of 40
Question Id: 1753
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Basement membrane
▨ Dysplastic cells

*Indicates active HPV infection.
HPV = human papillomavirus.

©UWorld

Human papillomavirus (HPV) infection of the cervical squamous epithelium can lead to dysplasia (ie, **cervical intraepithelial neoplasia** [CIN]), a **premalignant** lesion. Squamous **dysplasia** is characterized by a breakdown in the normal, organized progression from tall cells in the basal layer to flattened cells on the epithelial surface. Individual dysplastic cells are often pleomorphic (ie, differing in shape and size), have enlarged and hyperchromatic (ie, dark staining) nuclei, and are associated with numerous mitotic figures (normally found only in the basal layer). The grade of CIN describes the degree of epithelial disruption:

- **Low-grade CIN:** Dysplasia involves the lower third of the epithelium (ie, CIN 1)
- **High-grade CIN:** Dysplasia has advanced beyond the lower third of the epithelium (sometimes involving the entire thickness) but does not penetrate the basement membrane (ie, CIN 2 or 3)

In contrast to malignancy (eg, invasive carcinoma), dysplastic changes (if mild to moderate) **may reverse** when the causal factor is withdrawn. Most cases of low-grade CIN regress spontaneously once the **HPV infection** is **cleared** by the immune system.

(Choices A, B, C, D, and E) Abundant mitoses, disordered maturation, loss of cell polarity, nuclear abnormalities, and pleomorphism can be seen in both dysplasia and invasive carcinoma.

Educational objective:
Dysplasia, characterized by the disruption of organized epithelial cell differentiation with atypical cells, does not always progress to malignancy. Mild to moderate dysplastic changes may reverse when the causal factor is withdrawn.

Pathology	Pathology (General Principles)	Cervical cancer
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Block Time Elapsed: 00:13:06
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

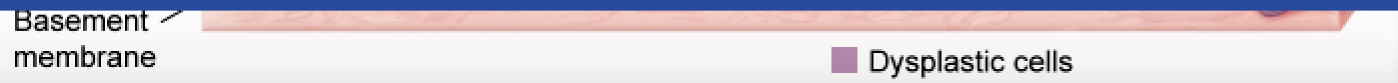

Basement membrane
Dysplastic cells

Exhibit Display

Human

intrae

in the

Individ

hyperc

the ba

- **L**
- **H**
  e

In con

causal

cleare

(Choic

and pl

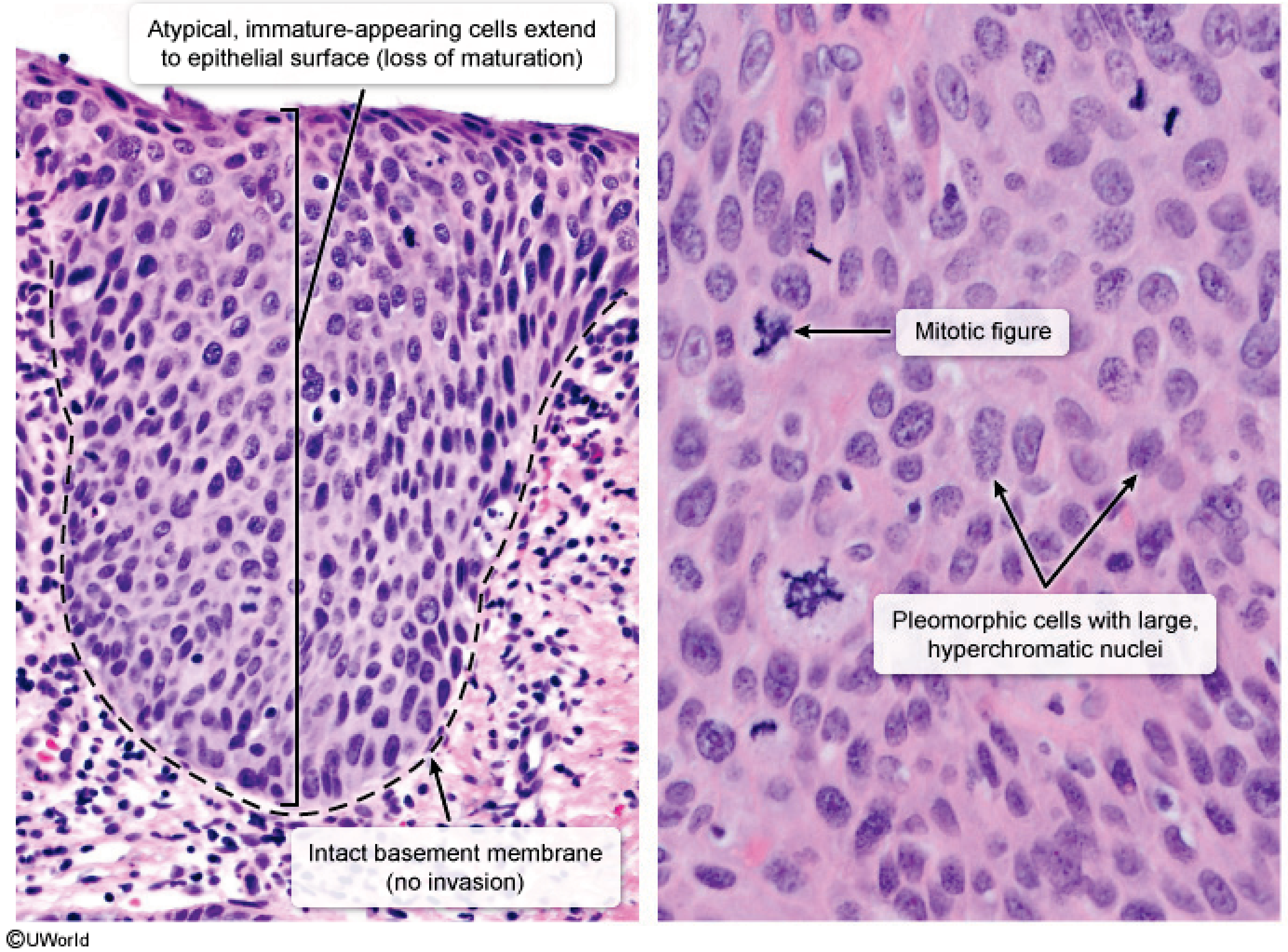
Educa

Dyspla

always

withdra

High-grade cervical intraepithelial neoplasia

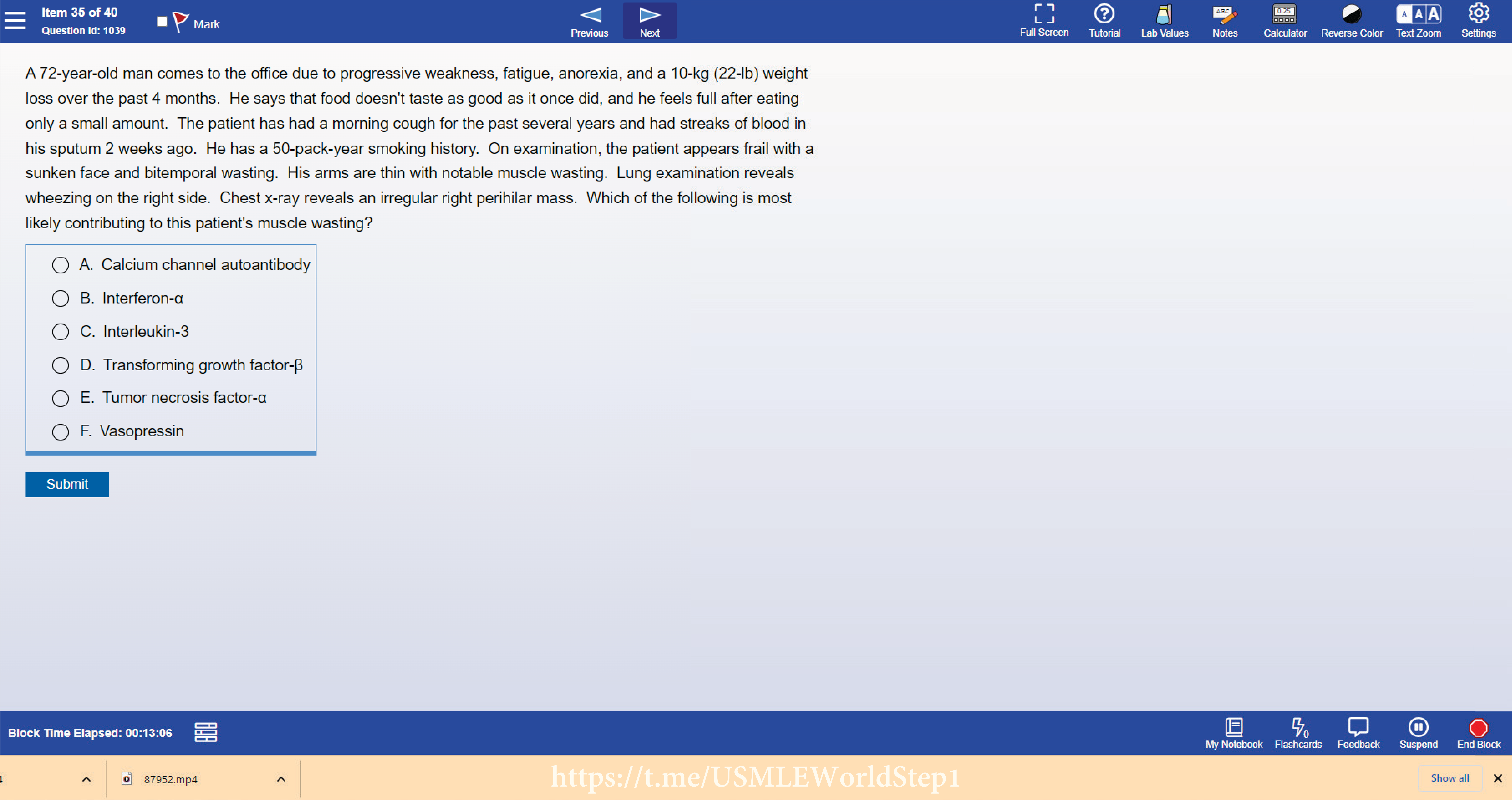

Atypical, immature-appearing cells extend to epithelial surface (loss of maturation)
Intact basement membrane (no invasion)
Mitotic figure
Pleomorphic cells with large, hyperchromatic nuclei
©UWorld

Zoom In   Zoom Out   Reset   New | Existing   My Notebook

Patholog

Subject

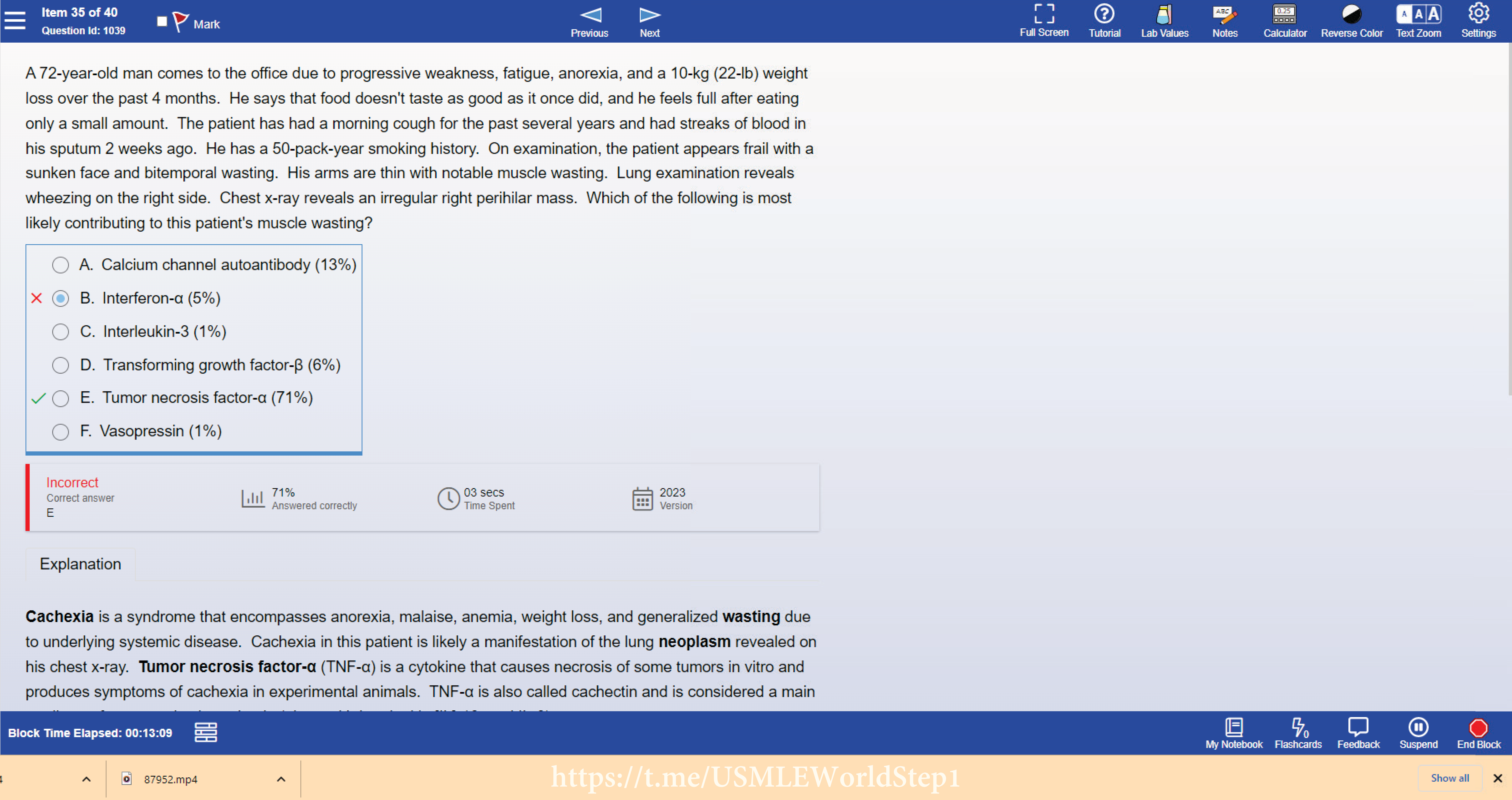
Copyright © UWorld. All rights reserved.


Item 35 of 40
Question Id: 1039
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 72-year-old man comes to the office due to progressive weakness, fatigue, anorexia, and a 10-kg (22-lb) weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

○ A. Calcium channel autoantibody
○ B. Interferon-α
○ C. Interleukin-3
○ D. Transforming growth factor-β
○ E. Tumor necrosis factor-α
○ F. Vasopressin

Submit
Block Time Elapsed: 00:13:06
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 35 of 40
Question Id: 1039
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 72-year-old man comes to the office due to progressive weakness, fatigue, anorexia, and a 10-kg (22-lb) weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

- ○ A. Calcium channel autoantibody (13%)
- ✗ ● B. Interferon-α (5%)
- ○ C. Interleukin-3 (1%)
- ○ D. Transforming growth factor-β (6%)
- ✓ ○ E. Tumor necrosis factor-α (71%)
- ○ F. Vasopressin (1%)

Incorrect
Correct answer
E

71%
Answered correctly

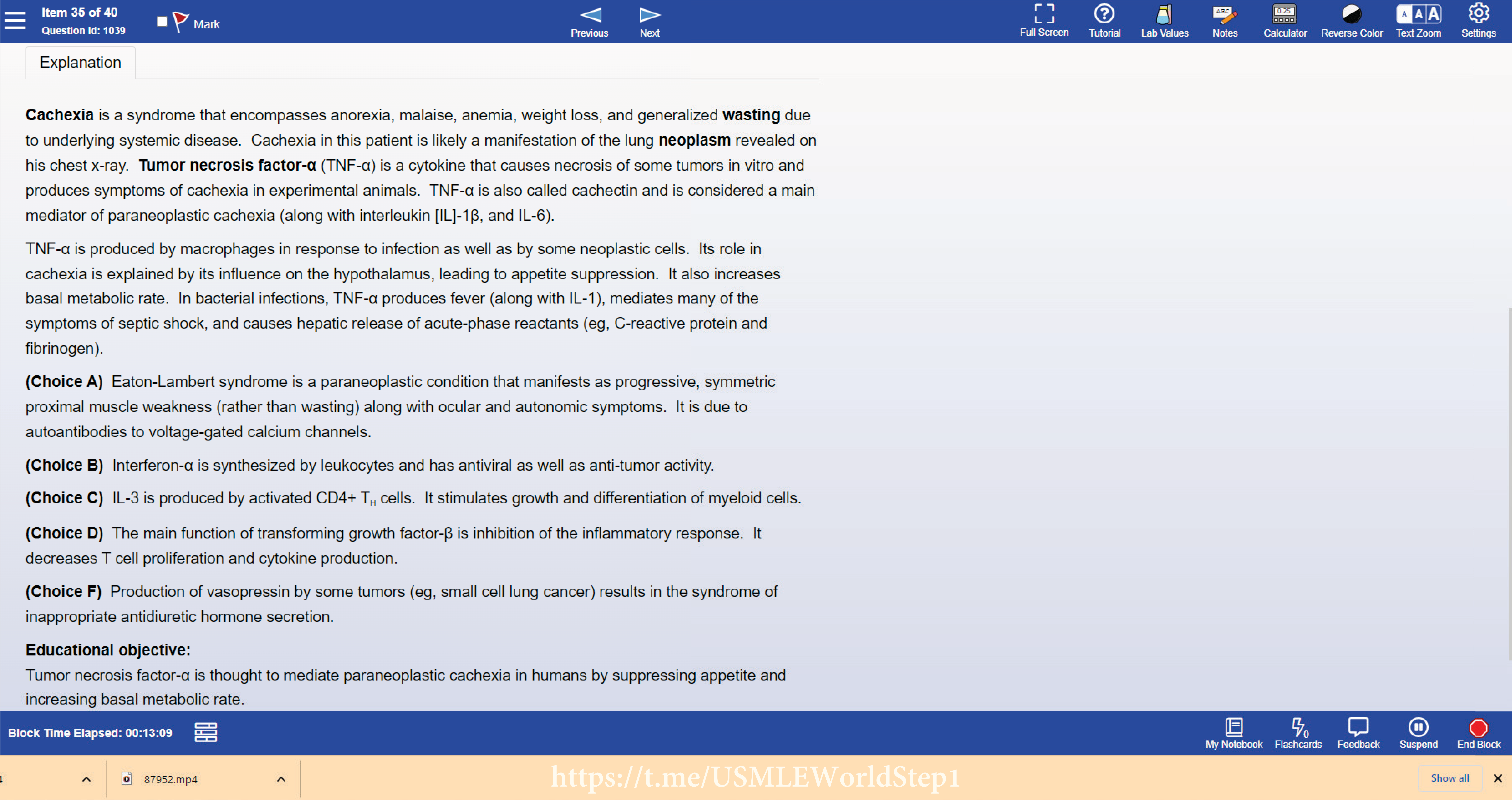
03 secs
Time Spent

2023
Version

Explanation

Cachexia is a syndrome that encompasses anorexia, malaise, anemia, weight loss, and generalized **wasting** due to underlying systemic disease. Cachexia in this patient is likely a manifestation of the lung **neoplasm** revealed on his chest x-ray. **Tumor necrosis factor-α** (TNF-α) is a cytokine that causes necrosis of some tumors in vitro and produces symptoms of cachexia in experimental animals. TNF-α is also called cachectin and is considered a main

Block Time Elapsed: 00:13:09
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 35 of 40
Question Id: 1039
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:13:09
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Explanation

Cachexia is a syndrome that encompasses anorexia, malaise, anemia, weight loss, and generalized **wasting** due to underlying systemic disease. Cachexia in this patient is likely a manifestation of the lung **neoplasm** revealed on his chest x-ray. **Tumor necrosis factor-α** (TNF-α) is a cytokine that causes necrosis of some tumors in vitro and produces symptoms of cachexia in experimental animals. TNF-α is also called cachectin and is considered a main mediator of paraneoplastic cachexia (along with interleukin [IL]-1β, and IL-6).

TNF-α is produced by macrophages in response to infection as well as by some neoplastic cells. Its role in cachexia is explained by its influence on the hypothalamus, leading to appetite suppression. It also increases basal metabolic rate. In bacterial infections, TNF-α produces fever (along with IL-1), mediates many of the symptoms of septic shock, and causes hepatic release of acute-phase reactants (eg, C-reactive protein and fibrinogen).

(Choice A) Eaton-Lambert syndrome is a paraneoplastic condition that manifests as progressive, symmetric proximal muscle weakness (rather than wasting) along with ocular and autonomic symptoms. It is due to autoantibodies to voltage-gated calcium channels.

(Choice B) Interferon-α is synthesized by leukocytes and has antiviral as well as anti-tumor activity.

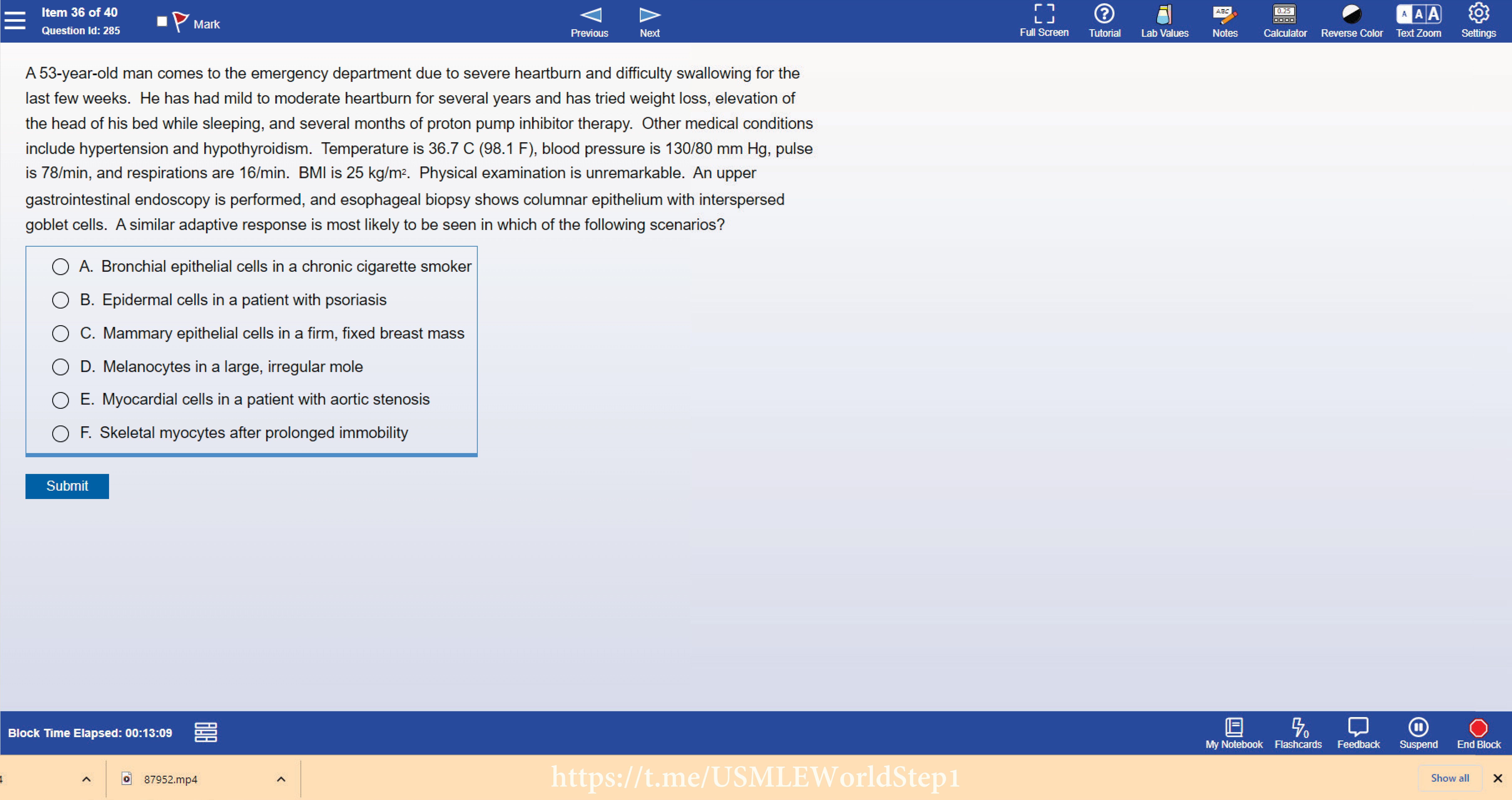
(Choice C) IL-3 is produced by activated CD4+ T_H cells. It stimulates growth and differentiation of myeloid cells.

(Choice D) The main function of transforming growth factor-β is inhibition of the inflammatory response. It decreases T cell proliferation and cytokine production.

(Choice F) Production of vasopressin by some tumors (eg, small cell lung cancer) results in the syndrome of inappropriate antidiuretic hormone secretion.

Educational objective:

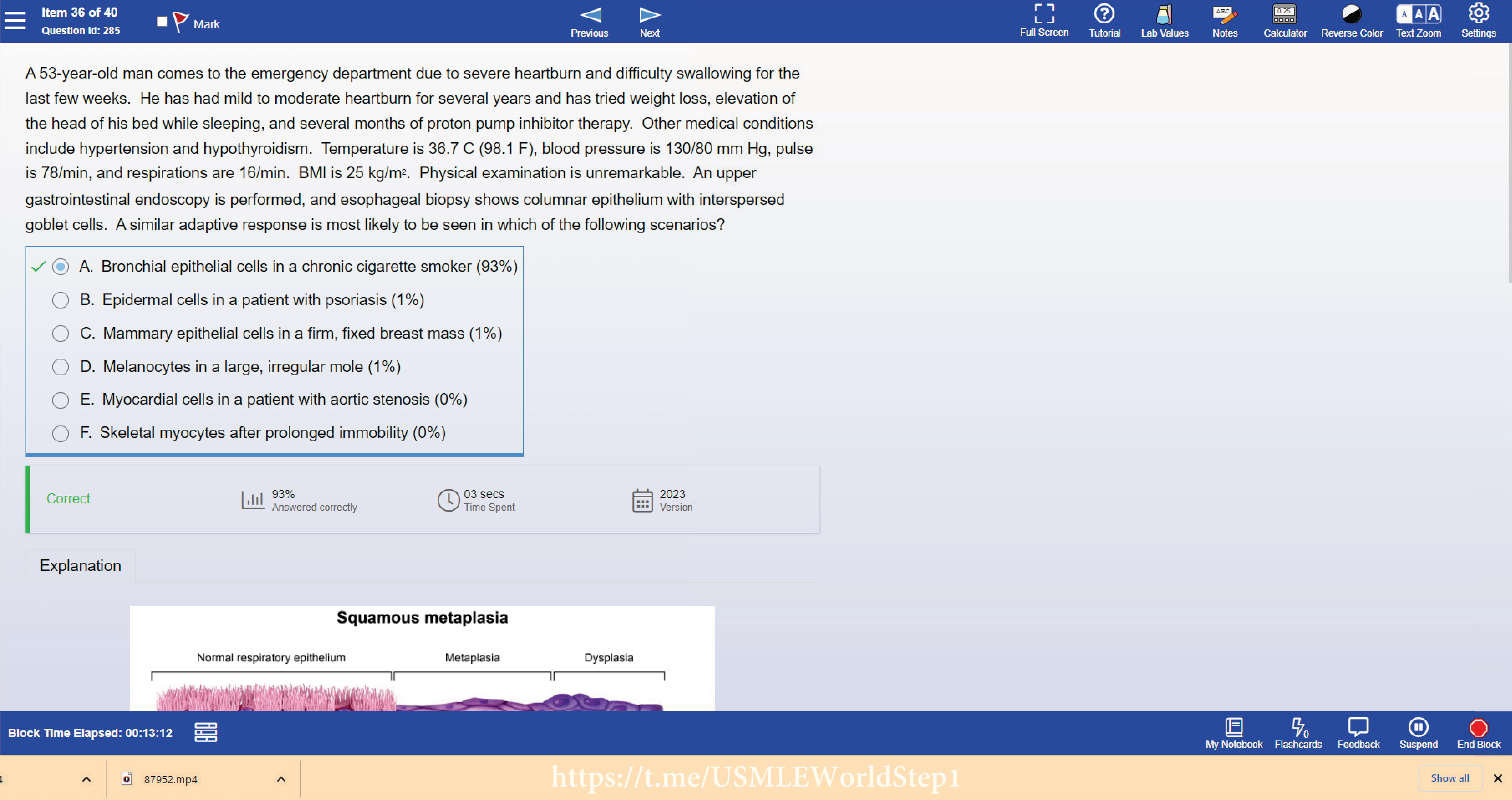
Tumor necrosis factor-α is thought to mediate paraneoplastic cachexia in humans by suppressing appetite and increasing basal metabolic rate.


Item 36 of 40
Question Id: 285
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 53-year-old man comes to the emergency department due to severe heartburn and difficulty swallowing for the last few weeks. He has had mild to moderate heartburn for several years and has tried weight loss, elevation of the head of his bed while sleeping, and several months of proton pump inhibitor therapy. Other medical conditions include hypertension and hypothyroidism. Temperature is 36.7 C (98.1 F), blood pressure is 130/80 mm Hg, pulse is 78/min, and respirations are 16/min. BMI is 25 kg/m^2. Physical examination is unremarkable. An upper gastrointestinal endoscopy is performed, and esophageal biopsy shows columnar epithelium with interspersed goblet cells. A similar adaptive response is most likely to be seen in which of the following scenarios?

○ A. Bronchial epithelial cells in a chronic cigarette smoker
○ B. Epidermal cells in a patient with psoriasis
○ C. Mammary epithelial cells in a firm, fixed breast mass
○ D. Melanocytes in a large, irregular mole
○ E. Myocardial cells in a patient with aortic stenosis
○ F. Skeletal myocytes after prolonged immobility

Submit
Block Time Elapsed: 00:13:09
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all



Item 36 of 40
Question Id: 285
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 53-year-old man comes to the emergency department due to severe heartburn and difficulty swallowing for the last few weeks. He has had mild to moderate heartburn for several years and has tried weight loss, elevation of the head of his bed while sleeping, and several months of proton pump inhibitor therapy. Other medical conditions include hypertension and hypothyroidism. Temperature is 36.7 C (98.1 F), blood pressure is 130/80 mm Hg, pulse is 78/min, and respirations are 16/min. BMI is 25 kg/m^2. Physical examination is unremarkable. An upper gastrointestinal endoscopy is performed, and esophageal biopsy shows columnar epithelium with interspersed goblet cells. A similar adaptive response is most likely to be seen in which of the following scenarios?

- ✓ ● A. Bronchial epithelial cells in a chronic cigarette smoker (93%)
- ○ B. Epidermal cells in a patient with psoriasis (1%)
- ○ C. Mammary epithelial cells in a firm, fixed breast mass (1%)
- ○ D. Melanocytes in a large, irregular mole (1%)
- ○ E. Myocardial cells in a patient with aortic stenosis (0%)
- ○ F. Skeletal myocytes after prolonged immobility (0%)

Correct

93% Answered correctly

03 secs Time Spent

2023 Version

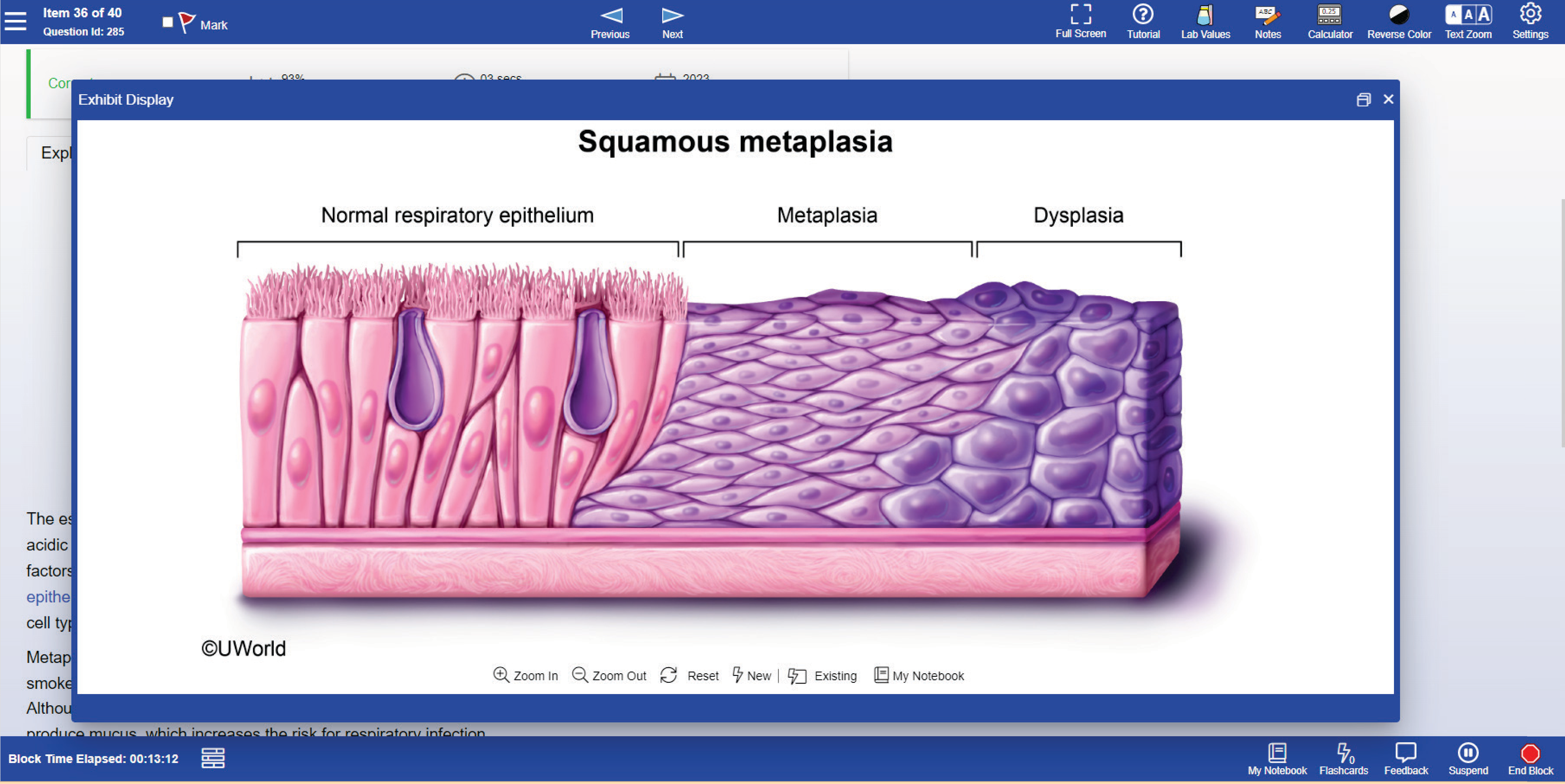
Explanation

Squamous metaplasia

Normal respiratory epithelium
Metaplasia
Dysplasia

Block Time Elapsed: 00:13:12

My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all


Item 36 of 40
Question Id: 285
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:13:12
My Notebook
Flashcards
Feedback
Suspend
End Block

Squamous metaplasia

Normal respiratory epithelium
Metaplasia
Dysplasia
©UWorld

The es

acidic

factors

epithe

cell typ

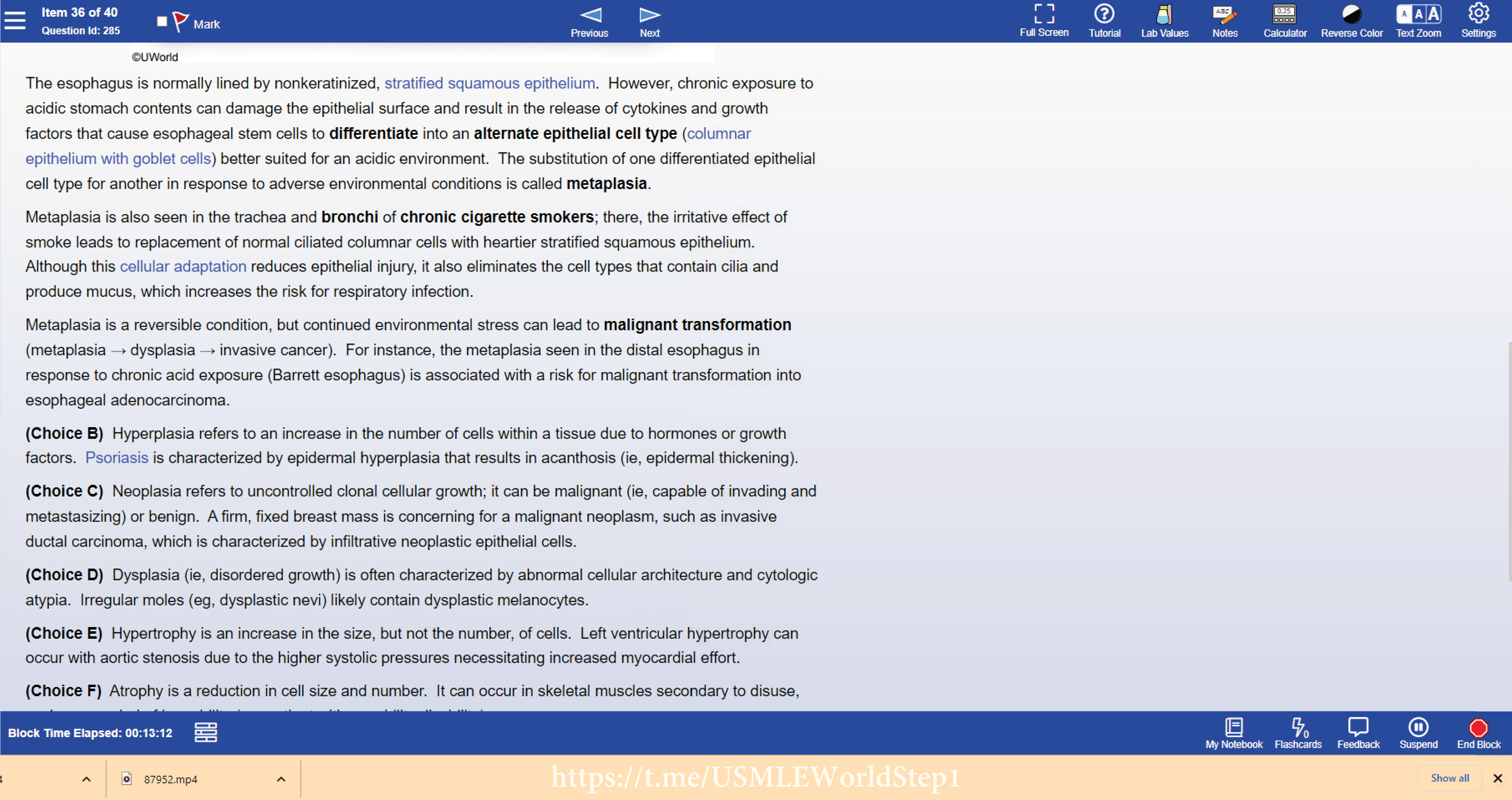
Metap

smoke

Althou

produce mucus, which increases the risk for respiratory infection.

87952.mp4
Show all



©UWorld

The esophagus is normally lined by nonkeratinized, stratified squamous epithelium. However, chronic exposure to acidic stomach contents can damage the epithelial surface and result in the release of cytokines and growth factors that cause esophageal stem cells to **differentiate** into an **alternate epithelial cell type** (columnar epithelium with goblet cells) better suited for an acidic environment. The substitution of one differentiated epithelial cell type for another in response to adverse environmental conditions is called **metaplasia**.

Metaplasia is also seen in the trachea and **bronchi** of **chronic cigarette smokers**; there, the irritative effect of smoke leads to replacement of normal ciliated columnar cells with heartier stratified squamous epithelium. Although this cellular adaptation reduces epithelial injury, it also eliminates the cell types that contain cilia and produce mucus, which increases the risk for respiratory infection.

Metaplasia is a reversible condition, but continued environmental stress can lead to **malignant transformation** (metaplasia → dysplasia → invasive cancer). For instance, the metaplasia seen in the distal esophagus in response to chronic acid exposure (Barrett esophagus) is associated with a risk for malignant transformation into esophageal adenocarcinoma.

(Choice B) Hyperplasia refers to an increase in the number of cells within a tissue due to hormones or growth factors. Psoriasis is characterized by epidermal hyperplasia that results in acanthosis (ie, epidermal thickening).

(Choice C) Neoplasia refers to uncontrolled clonal cellular growth; it can be malignant (ie, capable of invading and metastasizing) or benign. A firm, fixed breast mass is concerning for a malignant neoplasm, such as invasive ductal carcinoma, which is characterized by infiltrative neoplastic epithelial cells.

(Choice D) Dysplasia (ie, disordered growth) is often characterized by abnormal cellular architecture and cytologic atypia. Irregular moles (eg, dysplastic nevi) likely contain dysplastic melanocytes.

(Choice E) Hypertrophy is an increase in the size, but not the number, of cells. Left ventricular hypertrophy can occur with aortic stenosis due to the higher systolic pressures necessitating increased myocardial effort.

(Choice F) Atrophy is a reduction in cell size and number. It can occur in skeletal muscles secondary to disuse,

Item 36 of 40
Question Id: 285
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Metaplasia is also seen in the trachea and **bronchi** of **chronic cigarette smokers**; there, the irritative effect of smoke leads to replacement of normal ciliated columnar cells with heartier stratified squamous epithelium. Although this cellular adaptation reduces epithelial injury, it also eliminates the cell types that contain cilia and produce mucus, which increases the risk for respiratory infection.

Metaplasia is a reversible condition, but continued environmental stress can lead to **malignant transformation** (metaplasia → dysplasia → invasive cancer). For instance, the metaplasia seen in the distal esophagus in response to chronic acid exposure (Barrett esophagus) is associated with a risk for malignant transformation into esophageal adenocarcinoma.

(Choice B) Hyperplasia refers to an increase in the number of cells within a tissue due to hormones or growth factors. Psoriasis is characterized by epidermal hyperplasia that results in acanthosis (ie, epidermal thickening).

(Choice C) Neoplasia refers to uncontrolled clonal cellular growth; it can be malignant (ie, capable of invading and metastasizing) or benign. A firm, fixed breast mass is concerning for a malignant neoplasm, such as invasive ductal carcinoma, which is characterized by infiltrative neoplastic epithelial cells.

(Choice D) Dysplasia (ie, disordered growth) is often characterized by abnormal cellular architecture and cytologic atypia. Irregular moles (eg, dysplastic nevi) likely contain dysplastic melanocytes.

(Choice E) Hypertrophy is an increase in the size, but not the number, of cells. Left ventricular hypertrophy can occur with aortic stenosis due to the higher systolic pressures necessitating increased myocardial effort.

(Choice F) Atrophy is a reduction in cell size and number. It can occur in skeletal muscles secondary to disuse, such as a period of immobility (eg, patient with a mobility disability).

Educational objective:
Metaplasia is the substitution of one differentiated cell type for another in response to an adverse environmental stimulus. It is often seen in the bronchi of chronic cigarette smokers (ciliated columnar epithelium replaced by stratified squamous epithelium) and in the distal esophagus of patients with chronic gastroesophageal reflux (stratified squamous epithelium replaced by intestinal columnar epithelium).

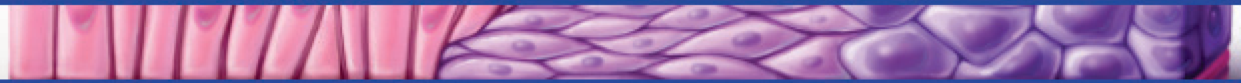
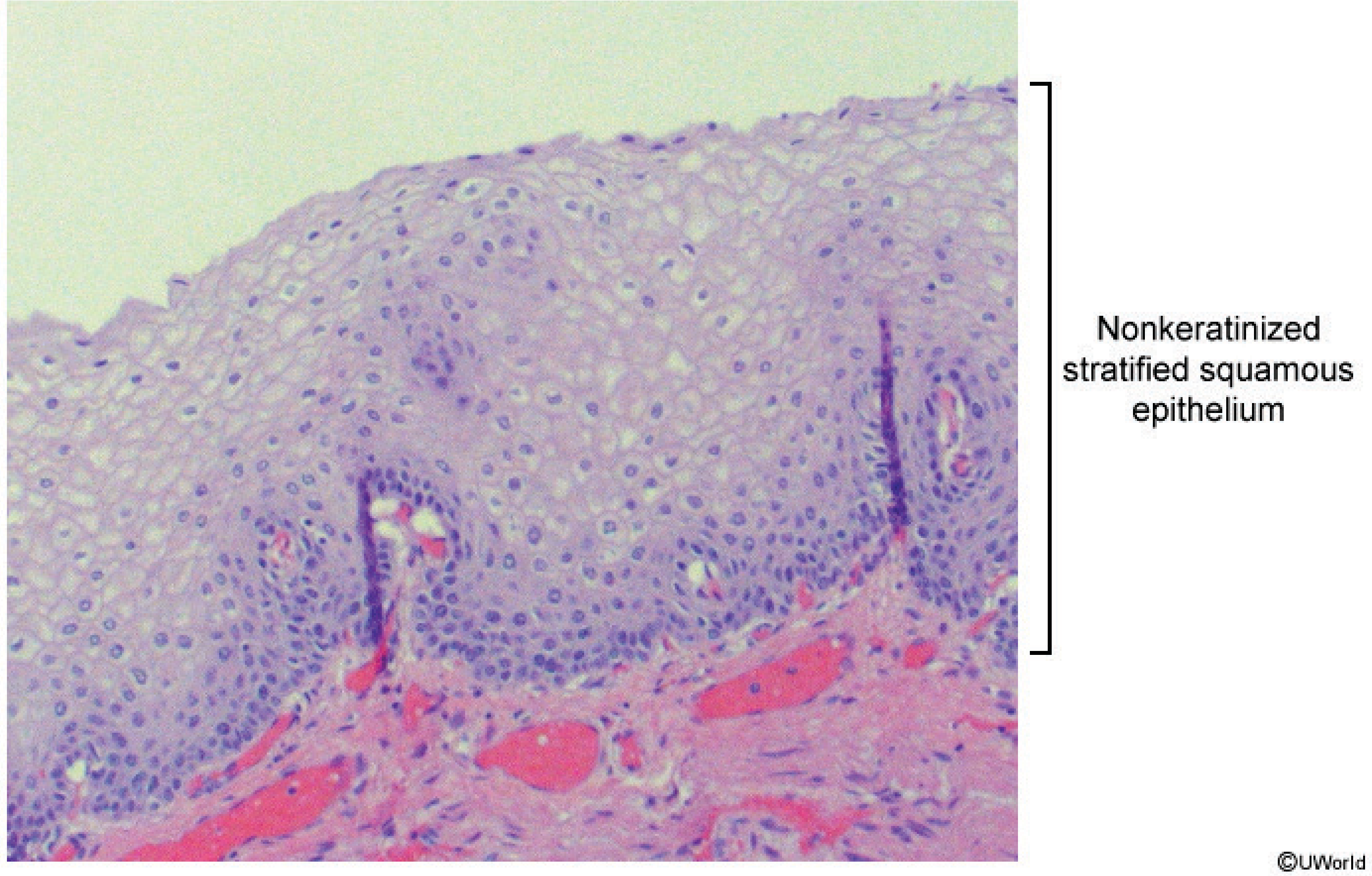


Exhibit Display

Normal esophagus


Nonkeratinized
stratified squamous
epithelium
©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

The es
acidic
factors
epithe
cell typ

Metap
smoke
Althou
produc

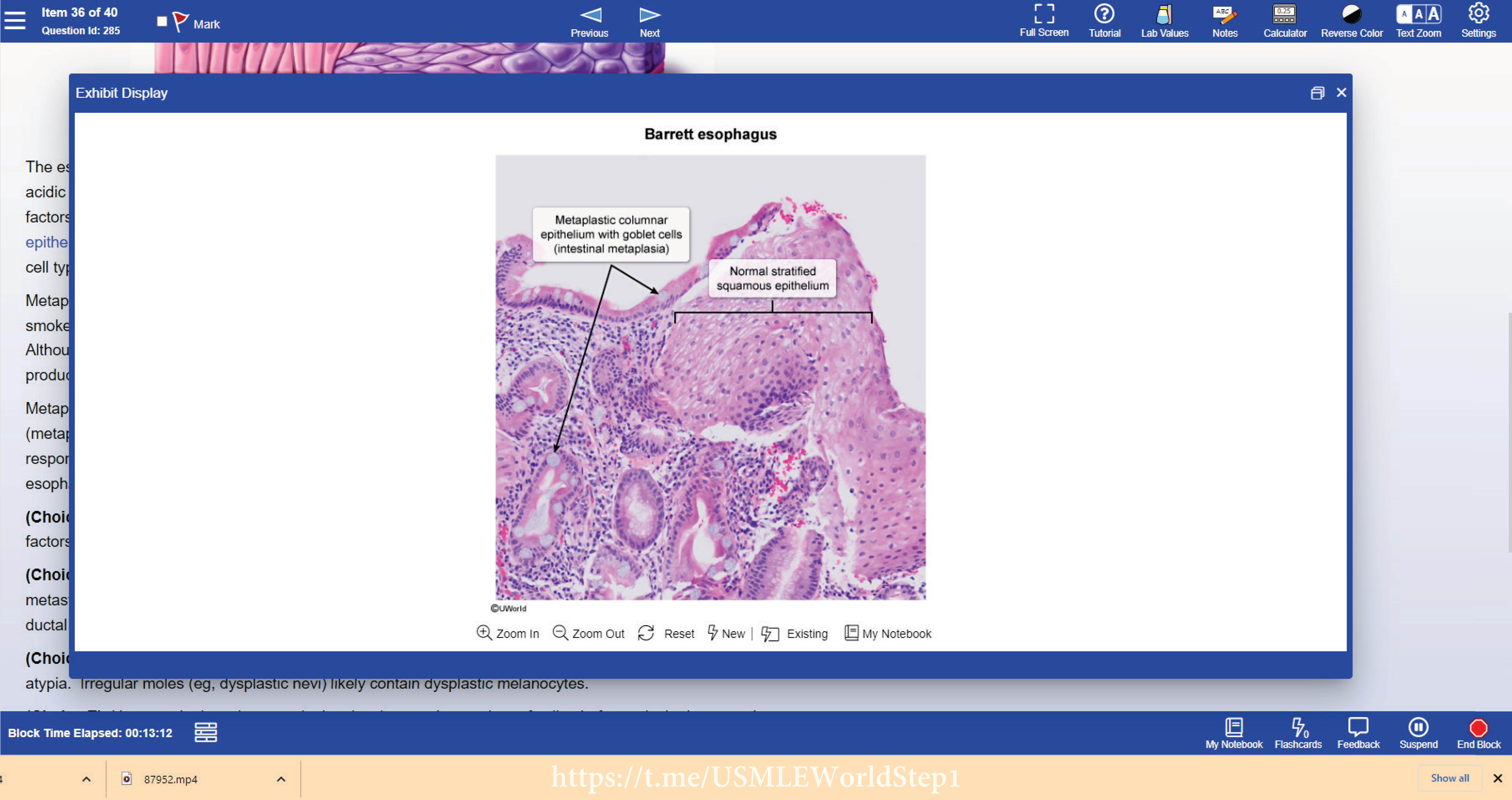
Metap
(metap
respor
esoph

(Choi
factors

(Choi
metas
ductal

(Choi
atypia. Irregular moles (eg, dysplastic nevi) likely contain dysplastic melanocytes.

87952.mp4
Show all


Item 36 of 40
Question Id: 285
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Metaplastic columnar epithelium with goblet cells (intestinal metaplasia)
Normal stratified squamous epithelium
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Block Time Elapsed: 00:13:12
My Notebook
Flashcards
Feedback
Suspend
End Block
87952.mp4
Show all

Barrett esophagus

©UWorld

The es
acidic
factors
epithe
cell typ

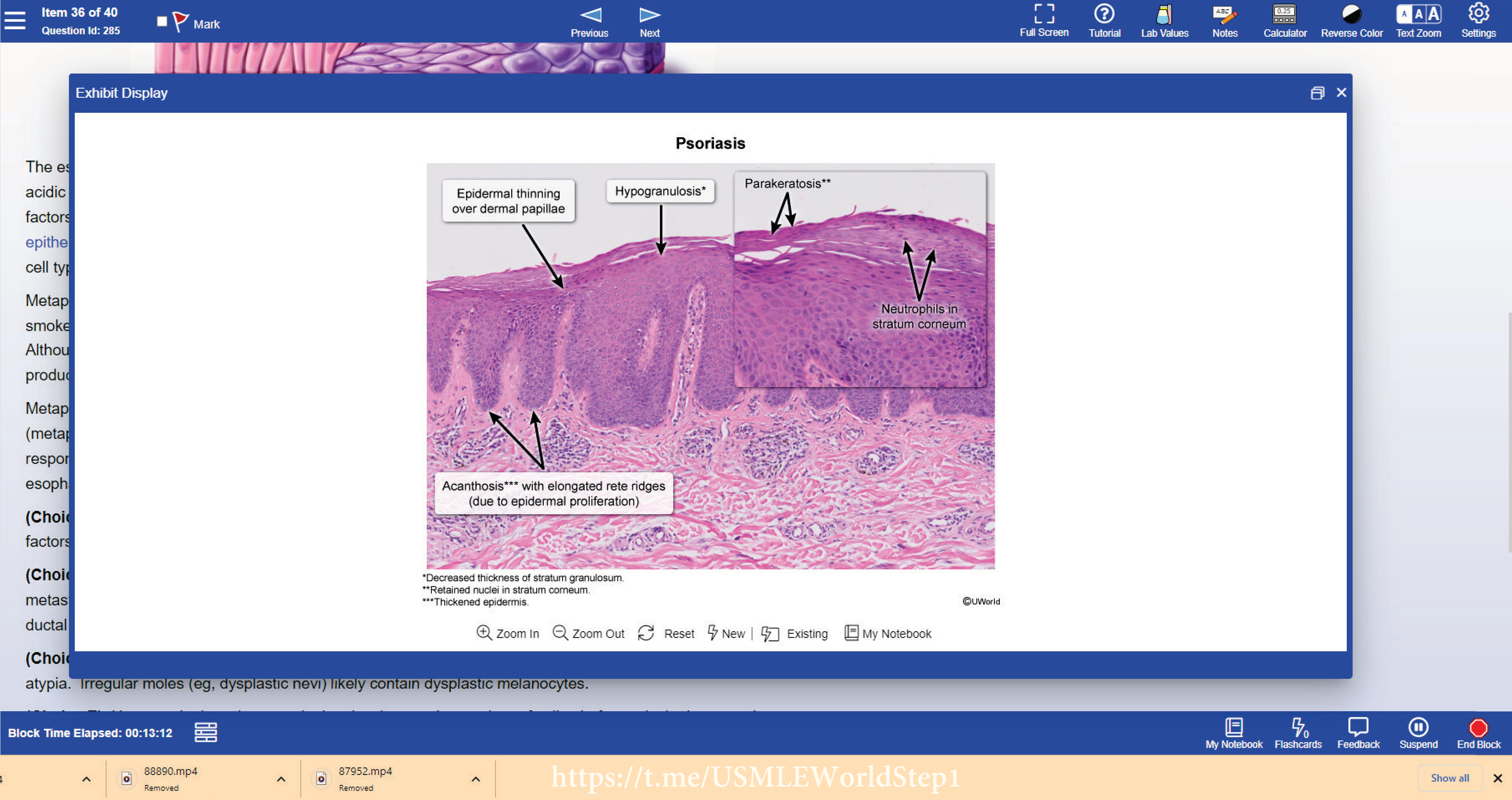
Metap
smoke
Althou
produ

Metap
(metap
respon
esoph

(Choi
factors

(Choi
metas
ductal

(Choi
atypia. Irregular moles (eg, dysplastic nevi) likely contain dysplastic melanocytes.


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
My Notebook
Flashcards
Feedback
Suspend
End Block
Show all

Item 36 of 40
Question Id: 285

Exhibit Display

Psoriasis

Epidermal thinning over dermal papillae
Hypogranulosis*
Parakeratosis**
Neutrophils in stratum corneum
Acanthosis*** with elongated rete ridges (due to epidermal proliferation)
©UWorld

*Decreased thickness of stratum granulosum.
**Retained nuclei in stratum corneum.
***Thickened epidermis.

The es
acidic
factors
epithe
cell typ

Metap
smoke
Althou
produc

Metap
(metap
respor
esoph

(Choi
factors

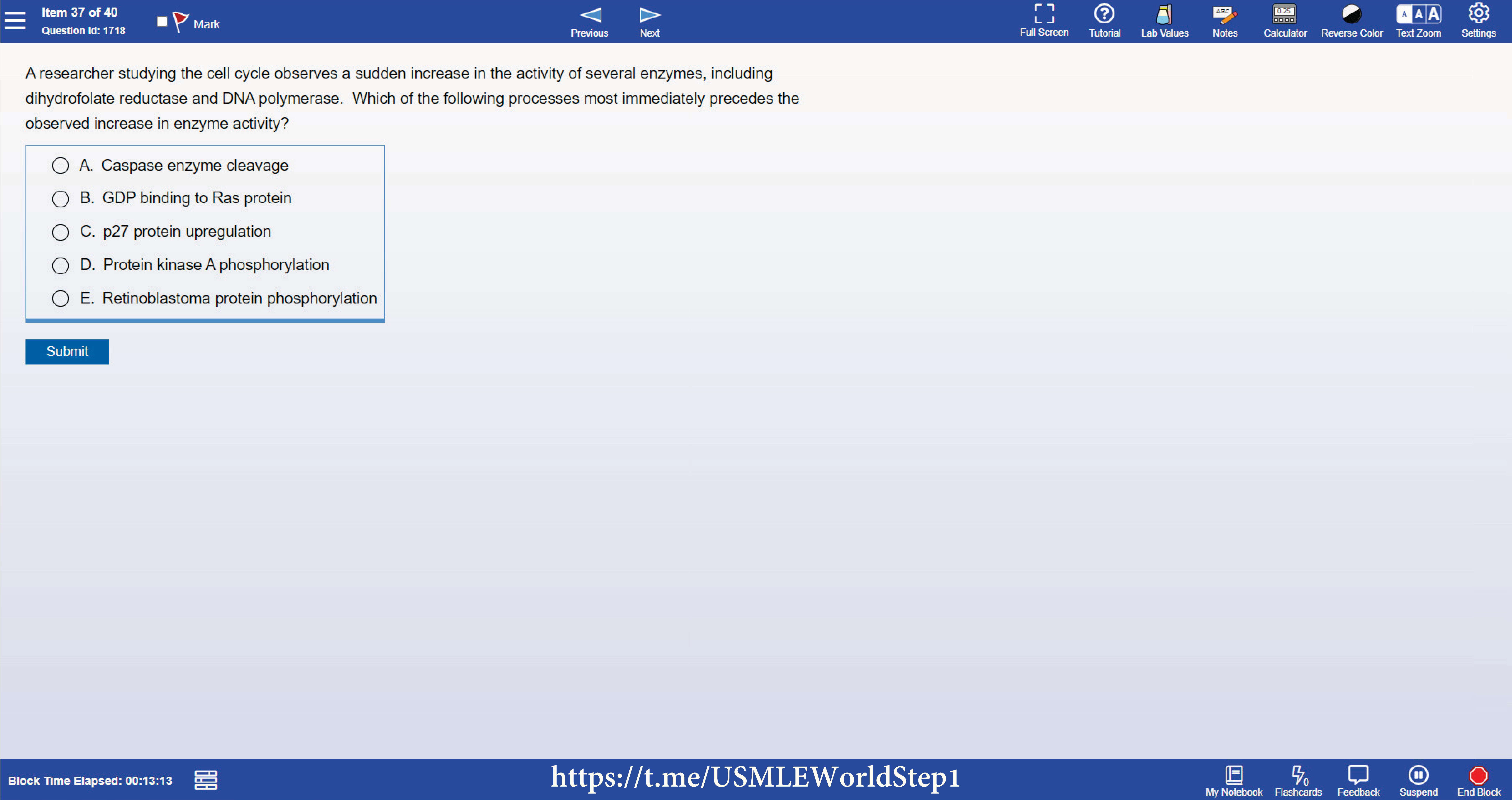
(Choi
metas
ductal

(Choi
atypia. Irregular moles (eg, dysplastic nevi) likely contain dysplastic melanocytes.

Block Time Elapsed: 00:13:12

88890.mp4
Removed

87952.mp4
Removed


Item 37 of 40
Question Id: 1718
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A researcher studying the cell cycle observes a sudden increase in the activity of several enzymes, including dihydrofolate reductase and DNA polymerase. Which of the following processes most immediately precedes the observed increase in enzyme activity?

○ A. Caspase enzyme cleavage
○ B. GDP binding to Ras protein
○ C. p27 protein upregulation
○ D. Protein kinase A phosphorylation
○ E. Retinoblastoma protein phosphorylation

Submit
Block Time Elapsed: 00:13:13
My Notebook
Flashcards
Feedback
Suspend
End Block

A researcher studying the cell cycle observes a sudden increase in the activity of several enzymes, including dihydrofolate reductase and DNA polymerase. Which of the following processes most immediately precedes the observed increase in enzyme activity?

- ○ A. Caspase enzyme cleavage (3%)
- ✗ ● B. GDP binding to Ras protein (15%)
- ○ C. p27 protein upregulation (7%)
- ○ D. Protein kinase A phosphorylation (16%)
- ✓ ○ E. Retinoblastoma protein phosphorylation (57%)

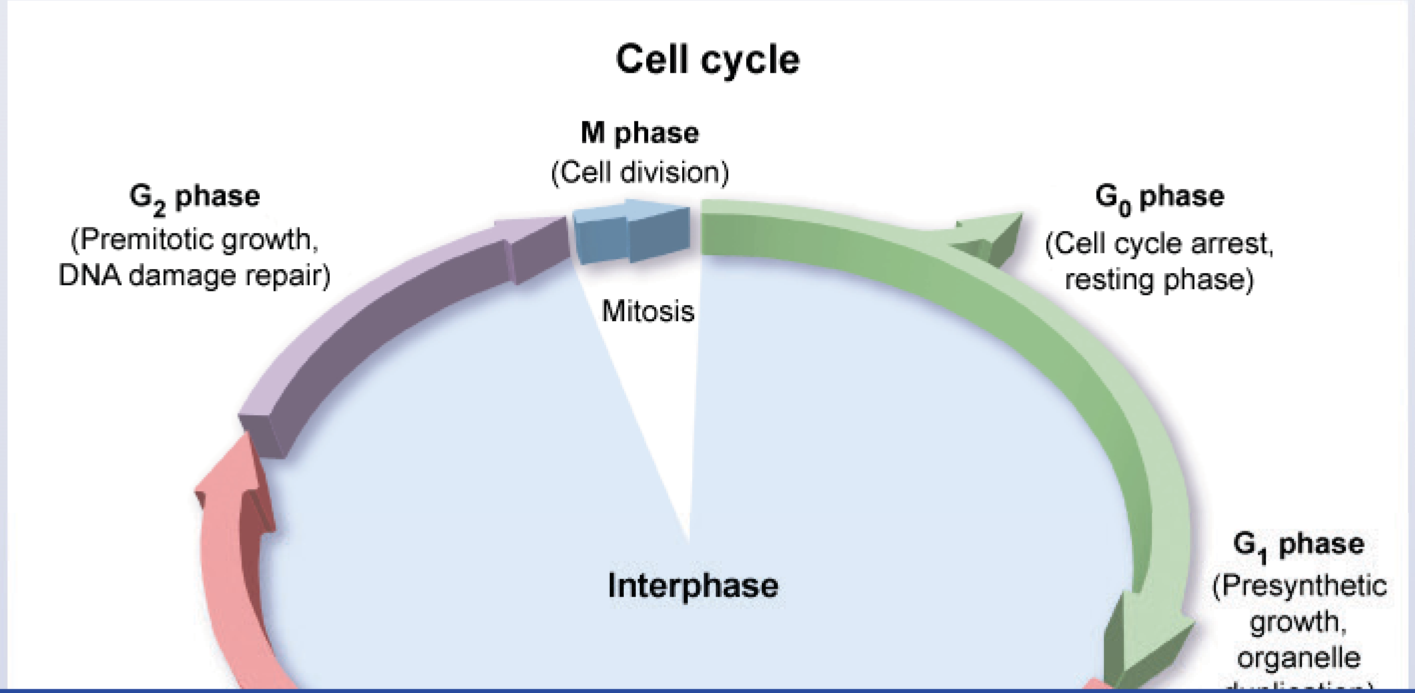
Incorrect
Correct answer
E

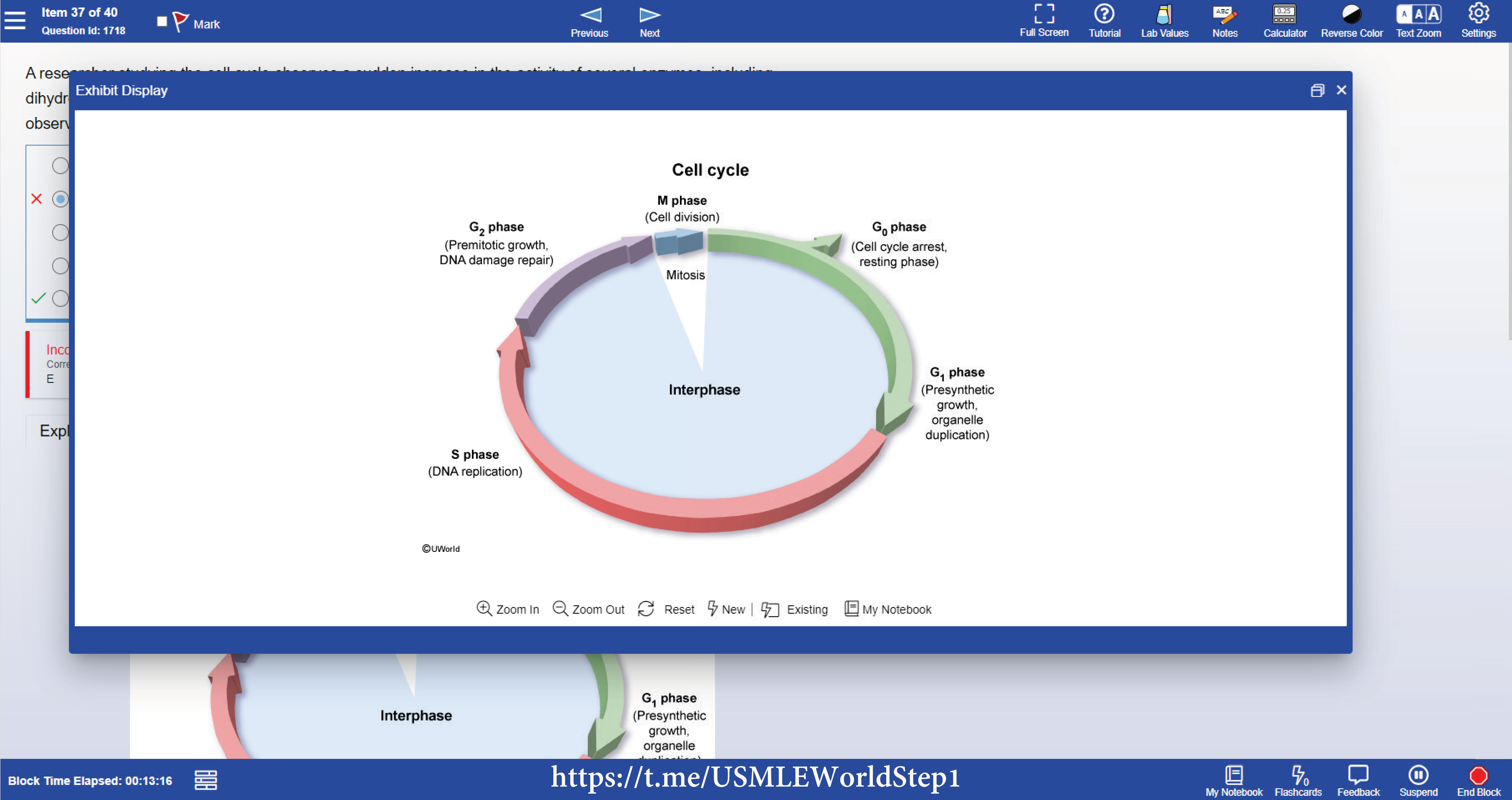
57%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation


Cell cycle
M phase
(Cell division)
G$_2$ phase
(Premitotic growth,
DNA damage repair)
G$_0$ phase
(Cell cycle arrest,
resting phase)
Mitosis
Interphase
G$_1$ phase
(Presynthetic
growth,
organelle

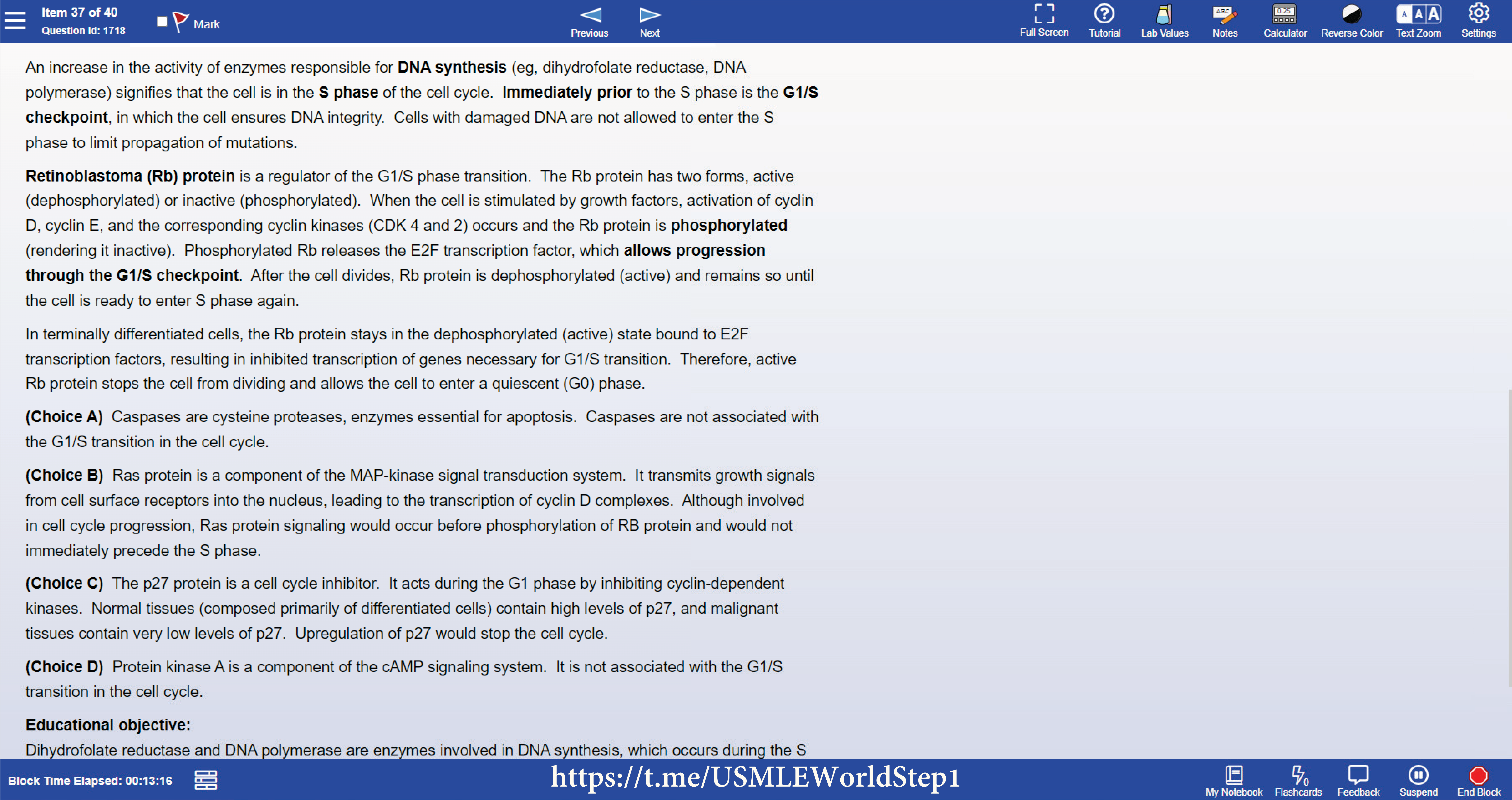

Item 37 of 40
Question Id: 1718
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A rese

dihydr

obser

○
○
○
○
○
Inco
Corre
E
Expl
Exhibit Display
Cell cycle
M phase
(Cell division)
G$_2$ phase
(Premitotic growth,
DNA damage repair)
G$_0$ phase
(Cell cycle arrest,
resting phase)
Mitosis
Interphase
G$_1$ phase
(Presynthetic
growth,
organelle
duplication)
S phase
(DNA replication)
©UWorld
Zoom In
Zoom Out
Reset
New
Existing
My Notebook
Interphase
G$_1$ phase
(Presynthetic
growth,
organelle
Block Time Elapsed: 00:13:16
My Notebook
Flashcards
Feedback
Suspend
End Block



An increase in the activity of enzymes responsible for **DNA synthesis** (eg, dihydrofolate reductase, DNA polymerase) signifies that the cell is in the **S phase** of the cell cycle. **Immediately prior** to the S phase is the **G1/S checkpoint**, in which the cell ensures DNA integrity. Cells with damaged DNA are not allowed to enter the S phase to limit propagation of mutations.

Retinoblastoma (Rb) protein is a regulator of the G1/S phase transition. The Rb protein has two forms, active (dephosphorylated) or inactive (phosphorylated). When the cell is stimulated by growth factors, activation of cyclin D, cyclin E, and the corresponding cyclin kinases (CDK 4 and 2) occurs and the Rb protein is **phosphorylated** (rendering it inactive). Phosphorylated Rb releases the E2F transcription factor, which **allows progression through the G1/S checkpoint**. After the cell divides, Rb protein is dephosphorylated (active) and remains so until the cell is ready to enter S phase again.

In terminally differentiated cells, the Rb protein stays in the dephosphorylated (active) state bound to E2F transcription factors, resulting in inhibited transcription of genes necessary for G1/S transition. Therefore, active Rb protein stops the cell from dividing and allows the cell to enter a quiescent (G0) phase.

(Choice A) Caspases are cysteine proteases, enzymes essential for apoptosis. Caspases are not associated with the G1/S transition in the cell cycle.

(Choice B) Ras protein is a component of the MAP-kinase signal transduction system. It transmits growth signals from cell surface receptors into the nucleus, leading to the transcription of cyclin D complexes. Although involved in cell cycle progression, Ras protein signaling would occur before phosphorylation of RB protein and would not immediately precede the S phase.

(Choice C) The p27 protein is a cell cycle inhibitor. It acts during the G1 phase by inhibiting cyclin-dependent kinases. Normal tissues (composed primarily of differentiated cells) contain high levels of p27, and malignant tissues contain very low levels of p27. Upregulation of p27 would stop the cell cycle.

(Choice D) Protein kinase A is a component of the cAMP signaling system. It is not associated with the G1/S transition in the cell cycle.

Educational objective:

Dihydrofolate reductase and DNA polymerase are enzymes involved in DNA synthesis, which occurs during the S phase to limit propagation of mutations.

Retinoblastoma (Rb) protein is a regulator of the G1/S phase transition. The Rb protein has two forms, active (dephosphorylated) or inactive (phosphorylated). When the cell is stimulated by growth factors, activation of cyclin D, cyclin E, and the corresponding cyclin kinases (CDK 4 and 2) occurs and the Rb protein is **phosphorylated** (rendering it inactive). Phosphorylated Rb releases the E2F transcription factor, which **allows progression through the G1/S checkpoint**. After the cell divides, Rb protein is dephosphorylated (active) and remains so until the cell is ready to enter S phase again.

In terminally differentiated cells, the Rb protein stays in the dephosphorylated (active) state bound to E2F transcription factors, resulting in inhibited transcription of genes necessary for G1/S transition. Therefore, active Rb protein stops the cell from dividing and allows the cell to enter a quiescent (G0) phase.

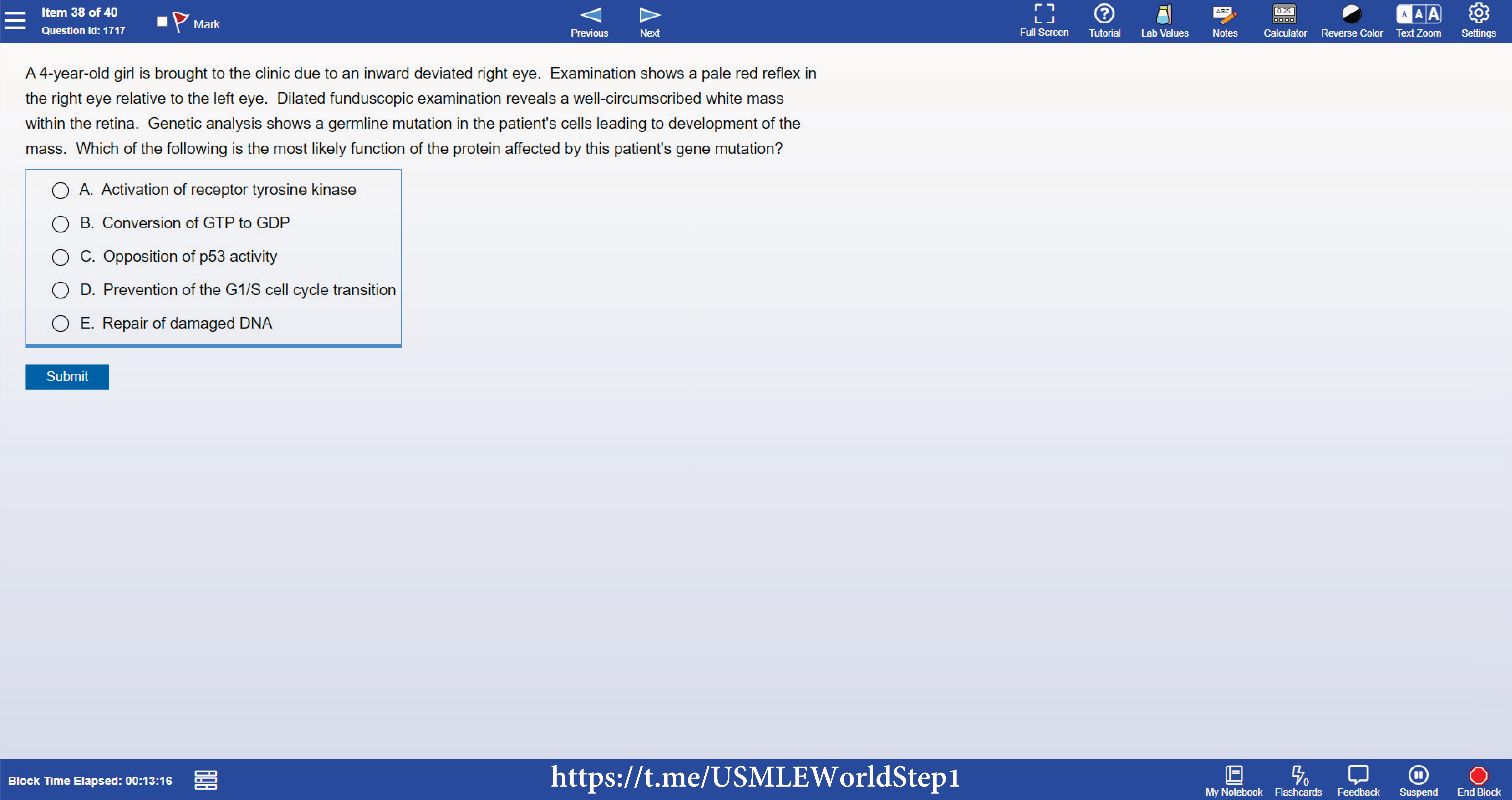
(Choice A) Caspases are cysteine proteases, enzymes essential for apoptosis. Caspases are not associated with the G1/S transition in the cell cycle.

(Choice B) Ras protein is a component of the MAP-kinase signal transduction system. It transmits growth signals from cell surface receptors into the nucleus, leading to the transcription of cyclin D complexes. Although involved in cell cycle progression, Ras protein signaling would occur before phosphorylation of RB protein and would not immediately precede the S phase.

(Choice C) The p27 protein is a cell cycle inhibitor. It acts during the G1 phase by inhibiting cyclin-dependent kinases. Normal tissues (composed primarily of differentiated cells) contain high levels of p27, and malignant tissues contain very low levels of p27. Upregulation of p27 would stop the cell cycle.

(Choice D) Protein kinase A is a component of the cAMP signaling system. It is not associated with the G1/S transition in the cell cycle.

Educational objective:
Dihydrofolate reductase and DNA polymerase are enzymes involved in DNA synthesis, which occurs during the S phase of the cell cycle. The Rb protein, in its active (dephosphorylated) form, regulates cell cycle progression by preventing the transition from the G1 phase to the S phase. Phosphorylation of the Rb protein inactivates it, allowing cells to progress through the G1/S checkpoint and proliferate.

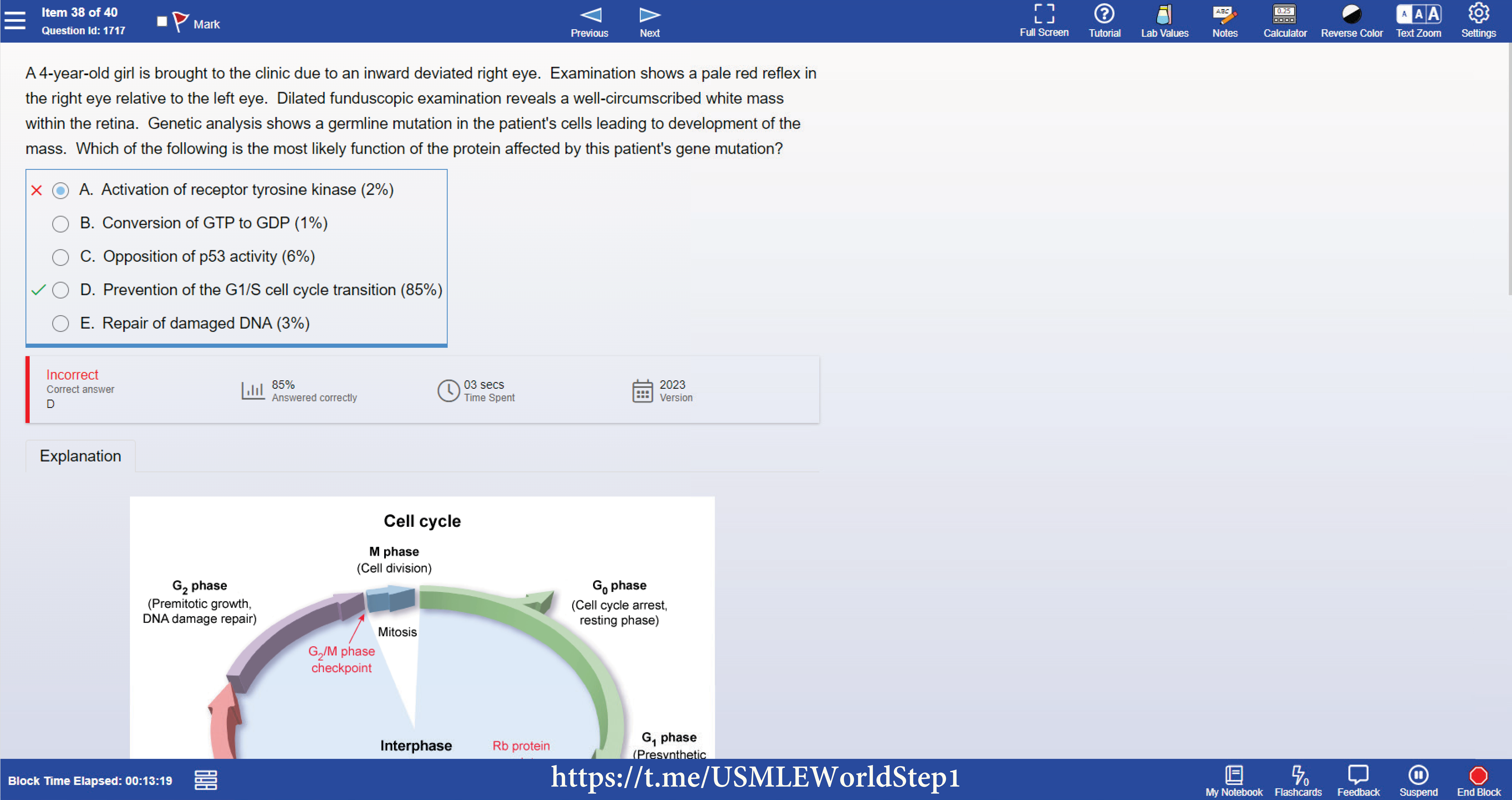

Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Submit
My Notebook
Flashcards
Feedback
Suspend
End Block

Item 38 of 40
Question Id: 1717

A 4-year-old girl is brought to the clinic due to an inward deviated right eye. Examination shows a pale red reflex in the right eye relative to the left eye. Dilated funduscopic examination reveals a well-circumscribed white mass within the retina. Genetic analysis shows a germline mutation in the patient's cells leading to development of the mass. Which of the following is the most likely function of the protein affected by this patient's gene mutation?

○ A. Activation of receptor tyrosine kinase
○ B. Conversion of GTP to GDP
○ C. Opposition of p53 activity
○ D. Prevention of the G1/S cell cycle transition
○ E. Repair of damaged DNA

Block Time Elapsed: 00:13:16


Item 38 of 40
Question Id: 1717
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 4-year-old girl is brought to the clinic due to an inward deviated right eye. Examination shows a pale red reflex in the right eye relative to the left eye. Dilated funduscopic examination reveals a well-circumscribed white mass within the retina. Genetic analysis shows a germline mutation in the patient's cells leading to development of the mass. Which of the following is the most likely function of the protein affected by this patient's gene mutation?

- ✗ ● A. Activation of receptor tyrosine kinase (2%)
- ○ B. Conversion of GTP to GDP (1%)
- ○ C. Opposition of p53 activity (6%)
- ✓ ○ D. Prevention of the G1/S cell cycle transition (85%)
- ○ E. Repair of damaged DNA (3%)

Incorrect
Correct answer
D

85%
Answered correctly

03 secs
Time Spent

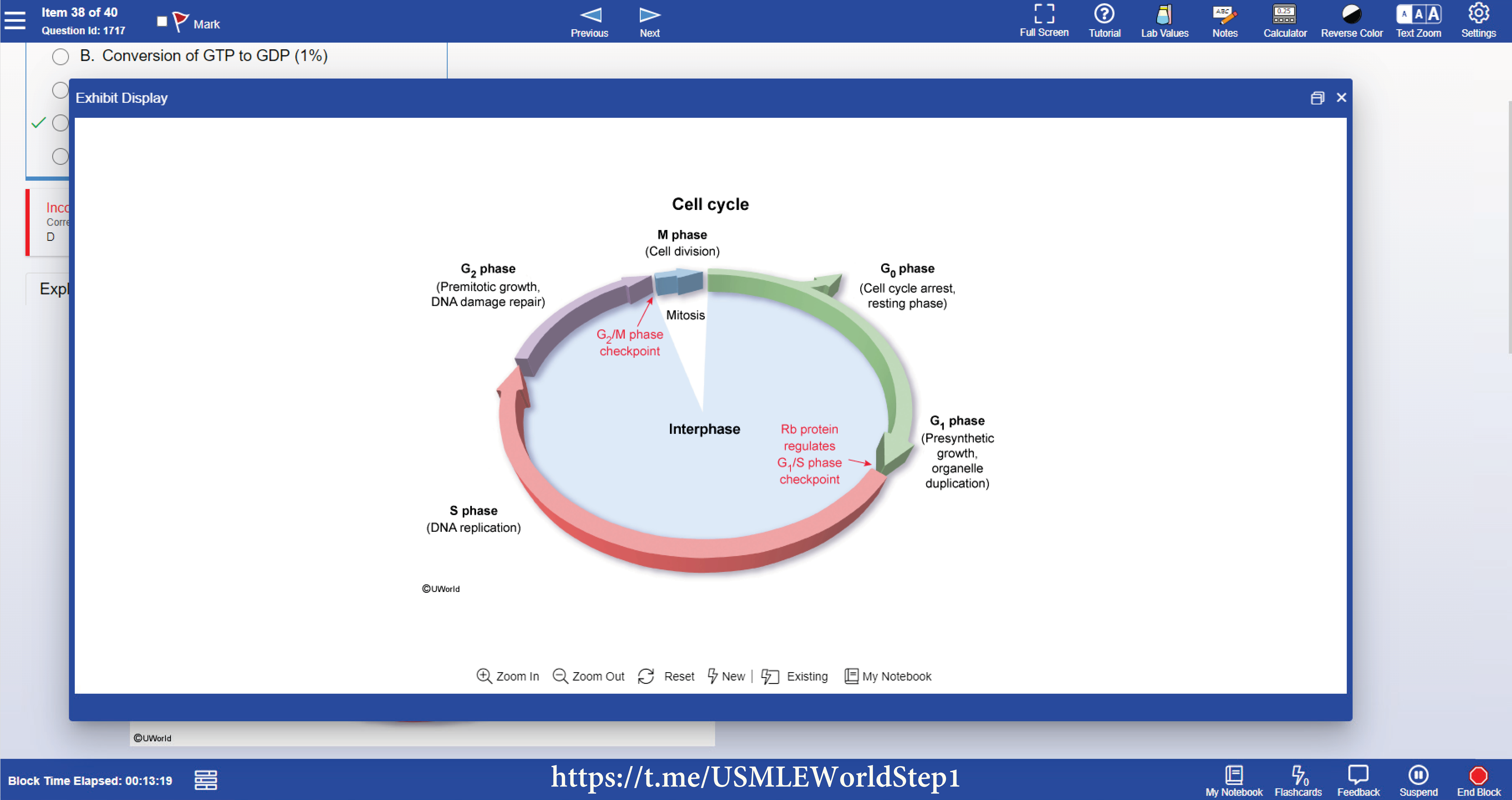
2023
Version

Explanation

Cell cycle

M phase
(Cell division)
G$_2$ phase
(Premitotic growth,
DNA damage repair)
G$_0$ phase
(Cell cycle arrest,
resting phase)
Mitosis
G$_2$/M phase
checkpoint
Interphase
Rb protein
G$_1$ phase
(Presynthetic

Block Time Elapsed: 00:13:19
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 38 of 40
Question Id: 1717
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Exhibit Display
Cell cycle
M phase
(Cell division)
G$_2$ phase
(Premitotic growth,
DNA damage repair)
G$_0$ phase
(Cell cycle arrest,
resting phase)
Mitosis
G$_2$/M phase
checkpoint
Interphase
Rb protein
regulates
G$_1$/S phase
checkpoint
G$_1$ phase
(Presynthetic
growth,
organelle
duplication)
S phase
(DNA replication)
©UWorld
Zoom In
Zoom Out
Reset
New |
Existing
My Notebook
©UWorld
My Notebook
Flashcards
Feedback
Suspend
End Block

○ B. Conversion of GTP to GDP (1%)

○

✓ ○

○

Inco
Corre
D

Expl

Block Time Elapsed: 00:13:19

©UWorld

This patient's pale red reflex and well-circumscribed white mass within the retina are indicative of **retinoblastoma**. Retinoblastoma is an intraocular tumor caused by inactivating mutations affecting the ***RB1*tumor suppressor gene** with subsequent dysregulation of the cell cycle.

The cell cycle consists of the following stages:

- Gap phase 0 (G0 phase) is a resting stage in which the cell cycle is suspended.
- Interphase is the stage in which the cell prepares for division. Interphase is subdivided into the G1 phase (synthesis of RNA, protein, lipid, and carbohydrate), S phase (DNA replication), and the G2 phase (ATP synthesis).
- Mitosis (M) is the stage in which the cell divides into two daughter cells.

Checkpoints occur at the G1/S and G2/M transitions, allowing the cell cycle to be stopped if damaged DNA is detected by cyclins and cyclin-dependent kinases. DNA repair mechanisms are activated, but if the DNA damage is too substantial, the cell undergoes apoptosis.

The ***RB1* gene** encodes the Rb protein that regulates the **G1/S checkpoint**. In its active form, Rb protein binds and inhibits E2F transcription factors, thereby halting the cell cycle. In contrast, when a cell is ready to divide, Rb protein is phosphorylated by cyclin-dependent kinases, allowing the cell to proceed through the G1/S checkpoint. **Loss-of-function** mutations affecting the Rb protein result in unrestricted progression through the G1/S checkpoint, leading to **uncontrolled cell division**. Inciting *RB1* mutations have been linked to retinoblastoma and **osteosarcoma**.

(Choice A) Many receptor tyrosine kinases have stimulatory effects on cell growth, and increased receptor activity occurs with a variety of cancers. For example, overexpression of *EGFR* and *MET* are associated with non–small cell lung cancer, and *HER2* is associated with breast cancer.

(Choice B) Abnormal K-Ras GTPase function due to a *KRAS* mutation prevents the conversion of GTP to GDP, which results in constant activation of the MAPK pathway and uncontrolled cellular proliferation. *KRAS* mutations are associated with lung and colorectal cancers, not retinoblastoma.

Item 38 of 40
Question Id: 1717
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

detected by cyclins and cyclin-dependent kinases. DNA repair mechanisms are activated, but if the DNA damage is too substantial, the cell undergoes apoptosis.

The ***RB1* gene** encodes the Rb protein that regulates the **G1/S checkpoint**. In its active form, Rb protein binds and inhibits E2F transcription factors, thereby halting the cell cycle. In contrast, when a cell is ready to divide, Rb protein is phosphorylated by cyclin-dependent kinases, allowing the cell to proceed through the G1/S checkpoint. **Loss-of-function** mutations affecting the Rb protein result in unrestricted progression through the G1/S checkpoint, leading to **uncontrolled cell division**. Inciting *RB1* mutations have been linked to retinoblastoma and **osteosarcoma**.

(Choice A) Many receptor tyrosine kinases have stimulatory effects on cell growth, and increased receptor activity occurs with a variety of cancers. For example, overexpression of *EGFR* and *MET* are associated with non–small cell lung cancer, and *HER2* is associated with breast cancer.

(Choice B) Abnormal K-Ras GTPase function due to a *KRAS* mutation prevents the conversion of GTP to GDP, which results in constant activation of the MAPK pathway and uncontrolled cellular proliferation. *KRAS* mutations are associated with lung and colorectal cancers, not retinoblastoma.

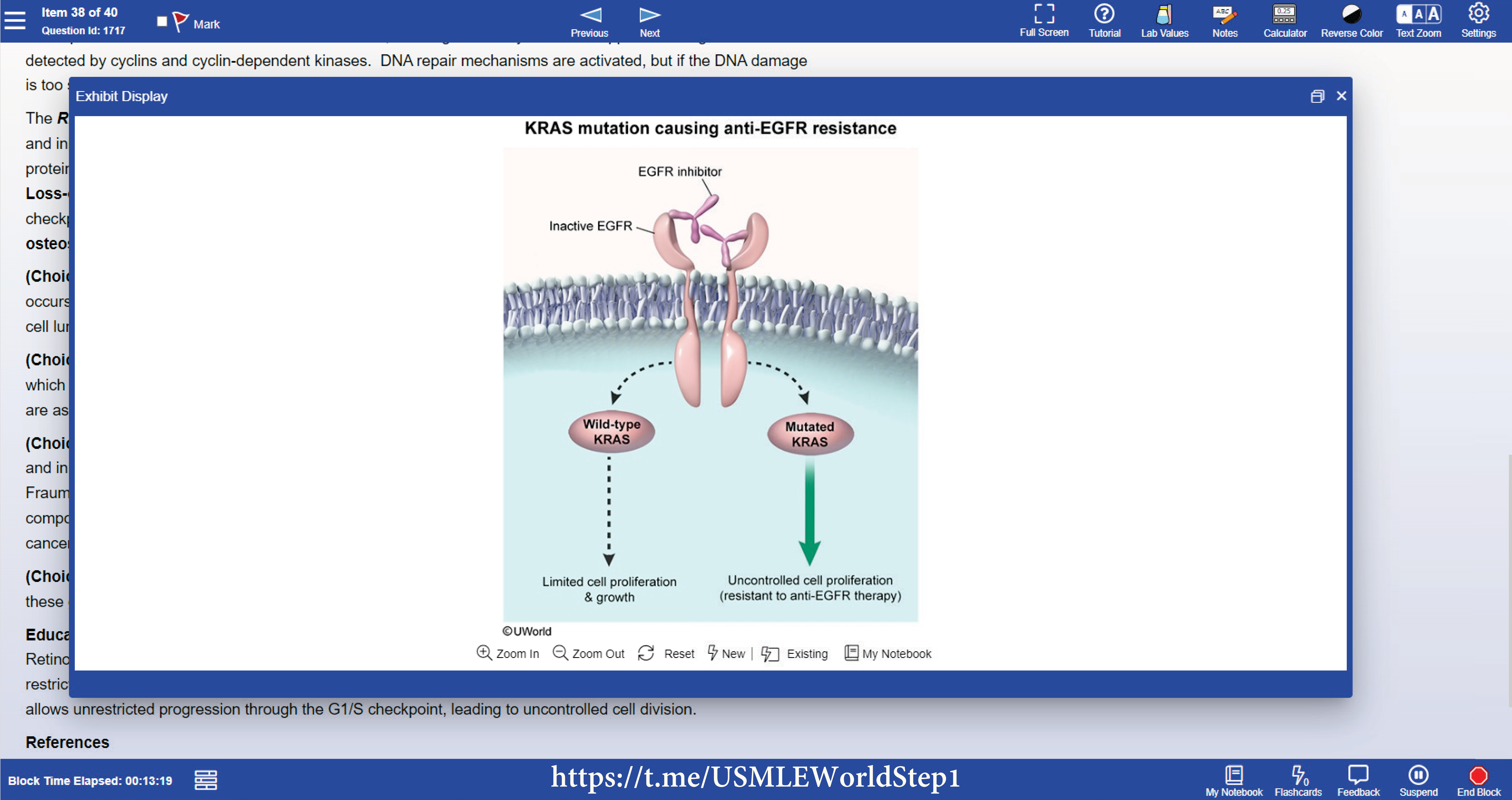
(Choice C) Tumor suppressor protein p53 arrests the cell cycle at the G1/S checkpoint if DNA damage is detected and initiates cell apoptosis if DNA repair fails. Mutations of p53 are associated with most cancers, particularly Li-Fraumeni syndrome (sarcoma, breast, leukemia, and adrenal cancers). Rb and p53 proteins are both critical components of tumor suppression pathways, and their normal function complements one another to prevent cancer progression.

(Choice E) *BRCA1* and *BRCA2* are two of many DNA repair genes that have been identified. When mutated, these genes are associated with an increased risk of breast and ovarian cancer.

Educational objective:

Retinoblastoma is associated with inactivating mutations of the *RB1* tumor suppressor gene, which normally restricts cells from passing the G1/S checkpoint until the cell is ready to divide. Impaired function of the Rb protein allows unrestricted progression through the G1/S checkpoint, leading to uncontrolled cell division.

References


Item 38 of 40
Question Id: 1717
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

detected by cyclins and cyclin-dependent kinases. DNA repair mechanisms are activated, but if the DNA damage
is too

The ***R***
and in
protei
Loss-
check
osteo

(Choi
occurs
cell lu

(Choi
which
are as

(Choi
and in
Fraum
compo
cance

(Choi
these

Educa
Retino
restric
allows unrestricted progression through the G1/S checkpoint, leading to uncontrolled cell division.

References

Exhibit Display

KRAS mutation causing anti-EGFR resistance

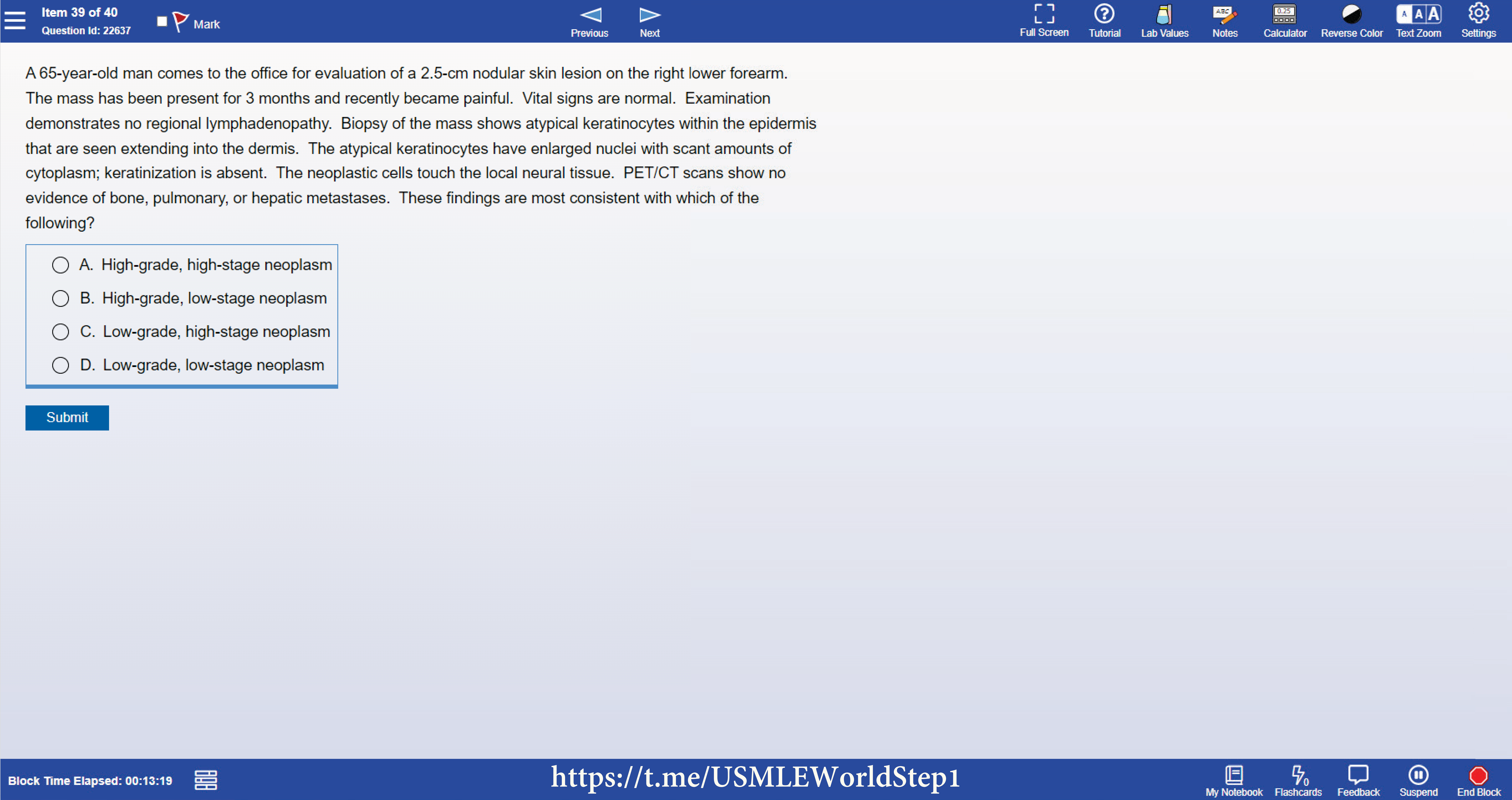
EGFR inhibitor
Inactive EGFR
Wild-type KRAS
Mutated KRAS
Limited cell proliferation & growth
Uncontrolled cell proliferation (resistant to anti-EGFR therapy)

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Block Time Elapsed: 00:13:19

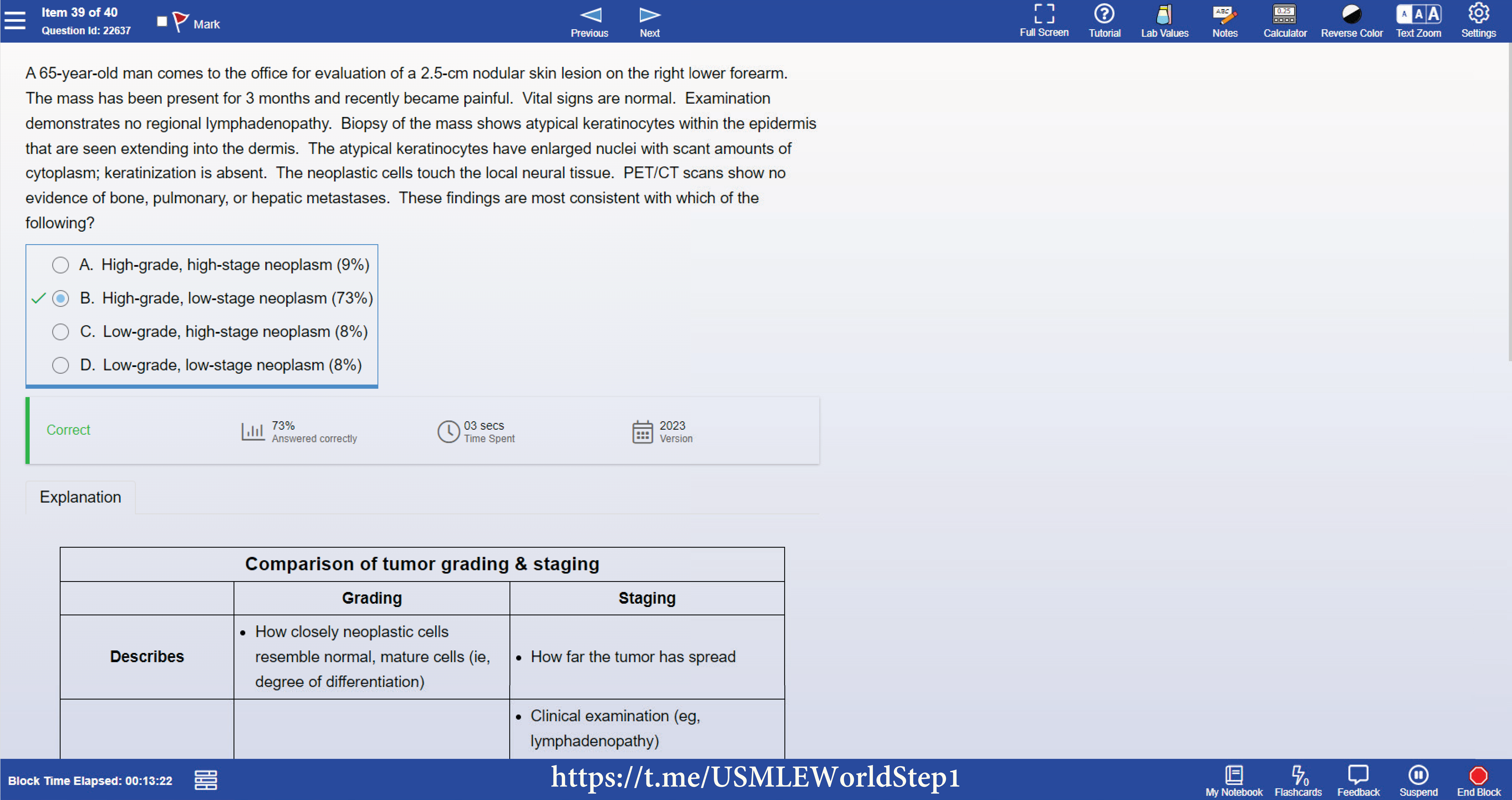
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 39 of 40
Question Id: 22637
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 65-year-old man comes to the office for evaluation of a 2.5-cm nodular skin lesion on the right lower forearm. The mass has been present for 3 months and recently became painful. Vital signs are normal. Examination demonstrates no regional lymphadenopathy. Biopsy of the mass shows atypical keratinocytes within the epidermis that are seen extending into the dermis. The atypical keratinocytes have enlarged nuclei with scant amounts of cytoplasm; keratinization is absent. The neoplastic cells touch the local neural tissue. PET/CT scans show no evidence of bone, pulmonary, or hepatic metastases. These findings are most consistent with which of the following?

○ A. High-grade, high-stage neoplasm
○ B. High-grade, low-stage neoplasm
○ C. Low-grade, high-stage neoplasm
○ D. Low-grade, low-stage neoplasm

Submit
Block Time Elapsed: 00:13:19
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 39 of 40
Question Id: 22637
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 65-year-old man comes to the office for evaluation of a 2.5-cm nodular skin lesion on the right lower forearm. The mass has been present for 3 months and recently became painful. Vital signs are normal. Examination demonstrates no regional lymphadenopathy. Biopsy of the mass shows atypical keratinocytes within the epidermis that are seen extending into the dermis. The atypical keratinocytes have enlarged nuclei with scant amounts of cytoplasm; keratinization is absent. The neoplastic cells touch the local neural tissue. PET/CT scans show no evidence of bone, pulmonary, or hepatic metastases. These findings are most consistent with which of the following?

○ A. High-grade, high-stage neoplasm (9%)
✓ ● B. High-grade, low-stage neoplasm (73%)
○ C. Low-grade, high-stage neoplasm (8%)
○ D. Low-grade, low-stage neoplasm (8%)

Correct

73% Answered correctly

03 secs Time Spent

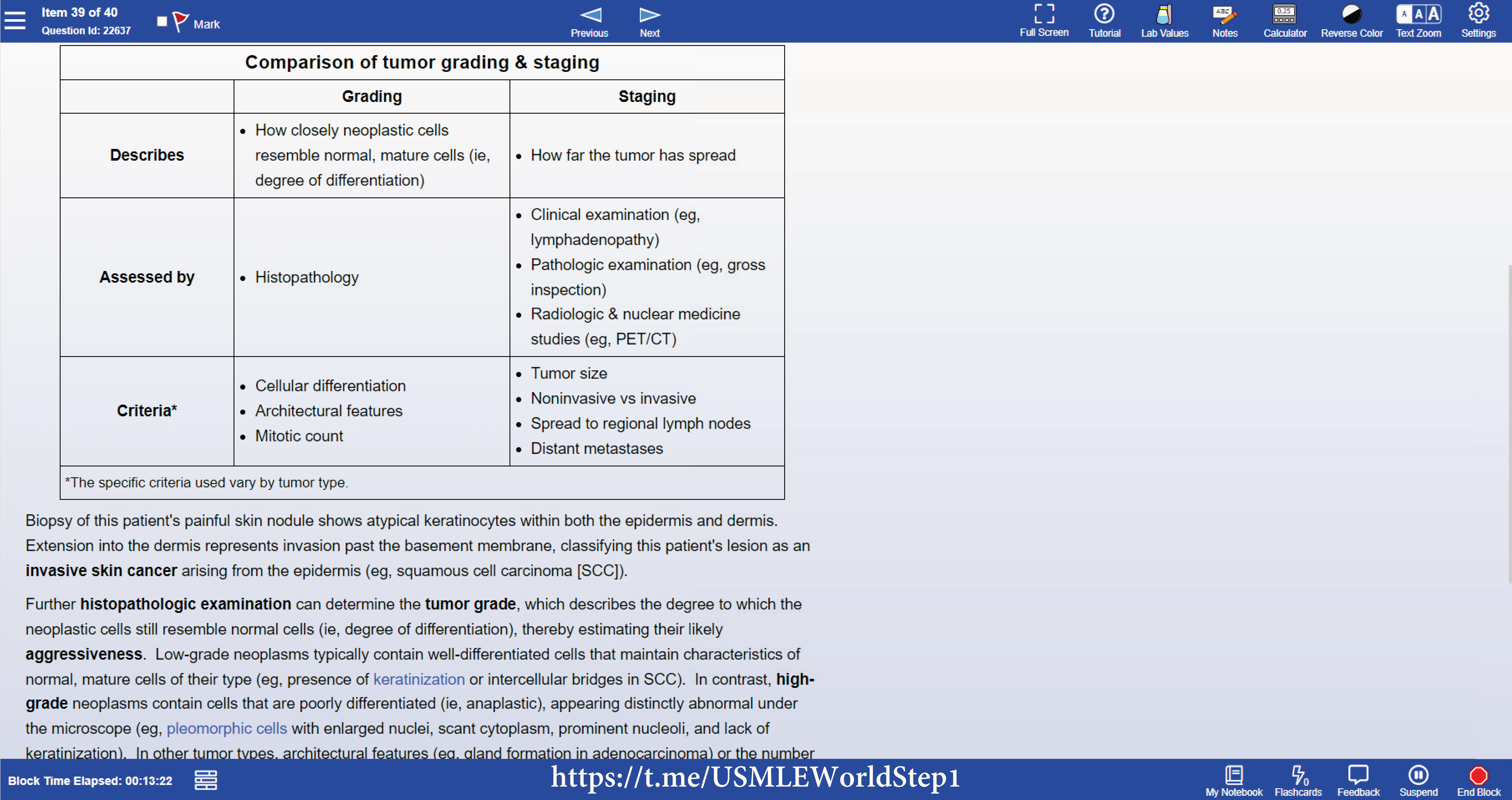
2023 Version

Explanation

Comparison of tumor grading & staging

	Grading	Staging
Describes	How closely neoplastic cells resemble normal, mature cells (ie, degree of differentiation)	How far the tumor has spread
		Clinical examination (eg, lymphadenopathy)

Block Time Elapsed: 00:13:22
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 39 of 40
Question Id: 22637
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

Comparison of tumor grading & staging

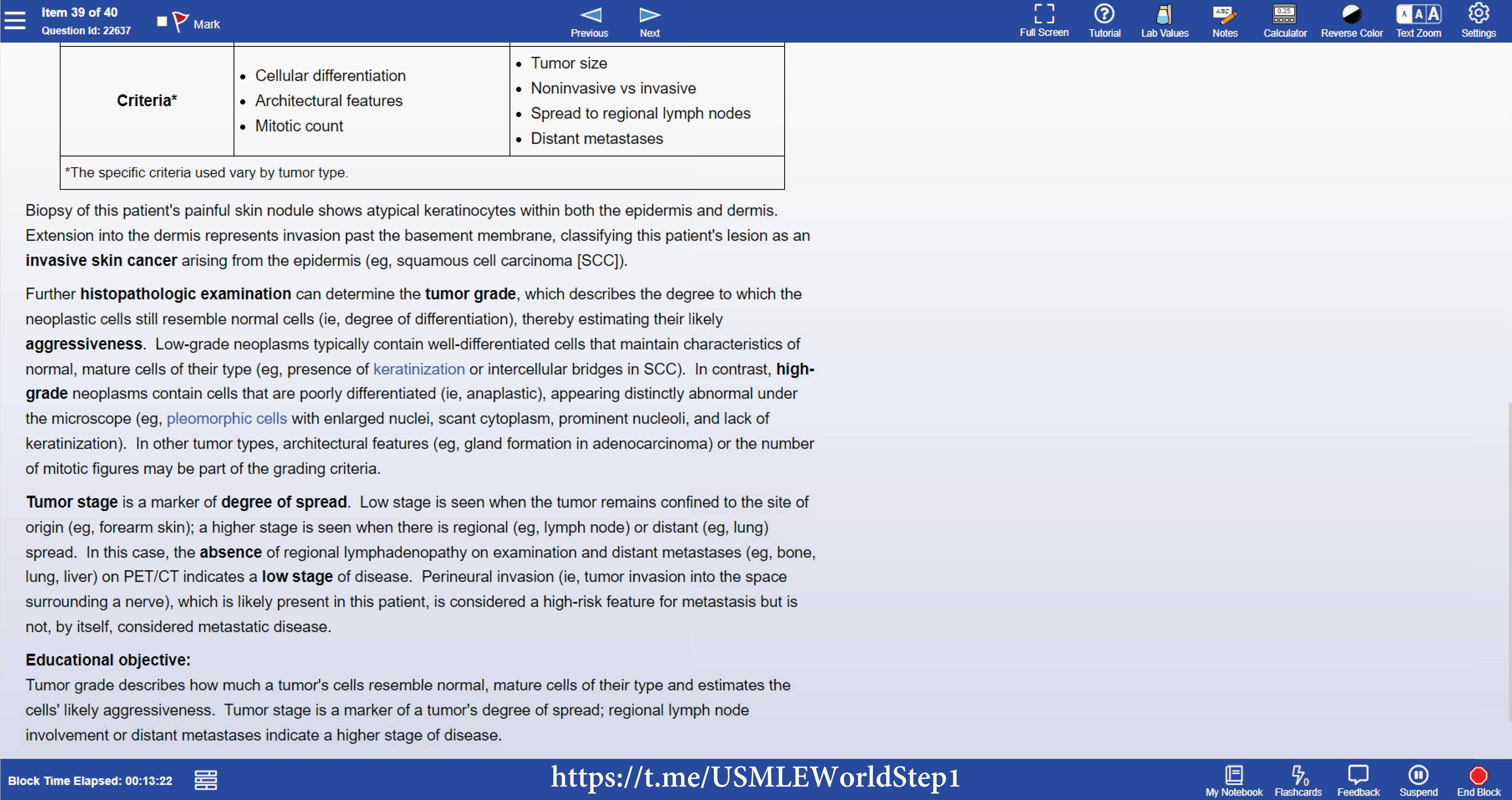
	Grading	Staging
Describes	• How closely neoplastic cells resemble normal, mature cells (ie, degree of differentiation)	• How far the tumor has spread
Assessed by	• Histopathology	• Clinical examination (eg, lymphadenopathy) • Pathologic examination (eg, gross inspection) • Radiologic & nuclear medicine studies (eg, PET/CT)
Criteria*	• Cellular differentiation • Architectural features • Mitotic count	• Tumor size • Noninvasive vs invasive • Spread to regional lymph nodes • Distant metastases

*The specific criteria used vary by tumor type.

Biopsy of this patient's painful skin nodule shows atypical keratinocytes within both the epidermis and dermis. Extension into the dermis represents invasion past the basement membrane, classifying this patient's lesion as an **invasive skin cancer** arising from the epidermis (eg, squamous cell carcinoma [SCC]).

Further **histopathologic examination** can determine the **tumor grade**, which describes the degree to which the neoplastic cells still resemble normal cells (ie, degree of differentiation), thereby estimating their likely **aggressiveness**. Low-grade neoplasms typically contain well-differentiated cells that maintain characteristics of normal, mature cells of their type (eg, presence of keratinization or intercellular bridges in SCC). In contrast, **high-grade** neoplasms contain cells that are poorly differentiated (ie, anaplastic), appearing distinctly abnormal under the microscope (eg, pleomorphic cells with enlarged nuclei, scant cytoplasm, prominent nucleoli, and lack of keratinization). In other tumor types, architectural features (eg, gland formation in adenocarcinoma) or the number

Block Time Elapsed: 00:13:22
My Notebook
Flashcards
Feedback
Suspend
End Block



Item 39 of 40
Question Id: 22637

Criteria*	Cellular differentiation Architectural features Mitotic count	Tumor size Noninvasive vs invasive Spread to regional lymph nodes Distant metastases
*The specific criteria used vary by tumor type.		

Biopsy of this patient's painful skin nodule shows atypical keratinocytes within both the epidermis and dermis. Extension into the dermis represents invasion past the basement membrane, classifying this patient's lesion as an **invasive skin cancer** arising from the epidermis (eg, squamous cell carcinoma [SCC]).

Further **histopathologic examination** can determine the **tumor grade**, which describes the degree to which the neoplastic cells still resemble normal cells (ie, degree of differentiation), thereby estimating their likely **aggressiveness**. Low-grade neoplasms typically contain well-differentiated cells that maintain characteristics of normal, mature cells of their type (eg, presence of keratinization or intercellular bridges in SCC). In contrast, **high-grade** neoplasms contain cells that are poorly differentiated (ie, anaplastic), appearing distinctly abnormal under the microscope (eg, pleomorphic cells with enlarged nuclei, scant cytoplasm, prominent nucleoli, and lack of keratinization). In other tumor types, architectural features (eg, gland formation in adenocarcinoma) or the number of mitotic figures may be part of the grading criteria.

Tumor stage is a marker of **degree of spread**. Low stage is seen when the tumor remains confined to the site of origin (eg, forearm skin); a higher stage is seen when there is regional (eg, lymph node) or distant (eg, lung) spread. In this case, the **absence** of regional lymphadenopathy on examination and distant metastases (eg, bone, lung, liver) on PET/CT indicates a **low stage** of disease. Perineural invasion (ie, tumor invasion into the space surrounding a nerve), which is likely present in this patient, is considered a high-risk feature for metastasis but is not, by itself, considered metastatic disease.

Educational objective:
Tumor grade describes how much a tumor's cells resemble normal, mature cells of their type and estimates the cells' likely aggressiveness. Tumor stage is a marker of a tumor's degree of spread; regional lymph node involvement or distant metastases indicate a higher stage of disease.

Block Time Elapsed: 00:13:22

- Mitotic count

- Distant metastases

Biopsy
Extens
invasi

Furthe
neopla
aggre
norma
grade
the mi
keratir
of mito

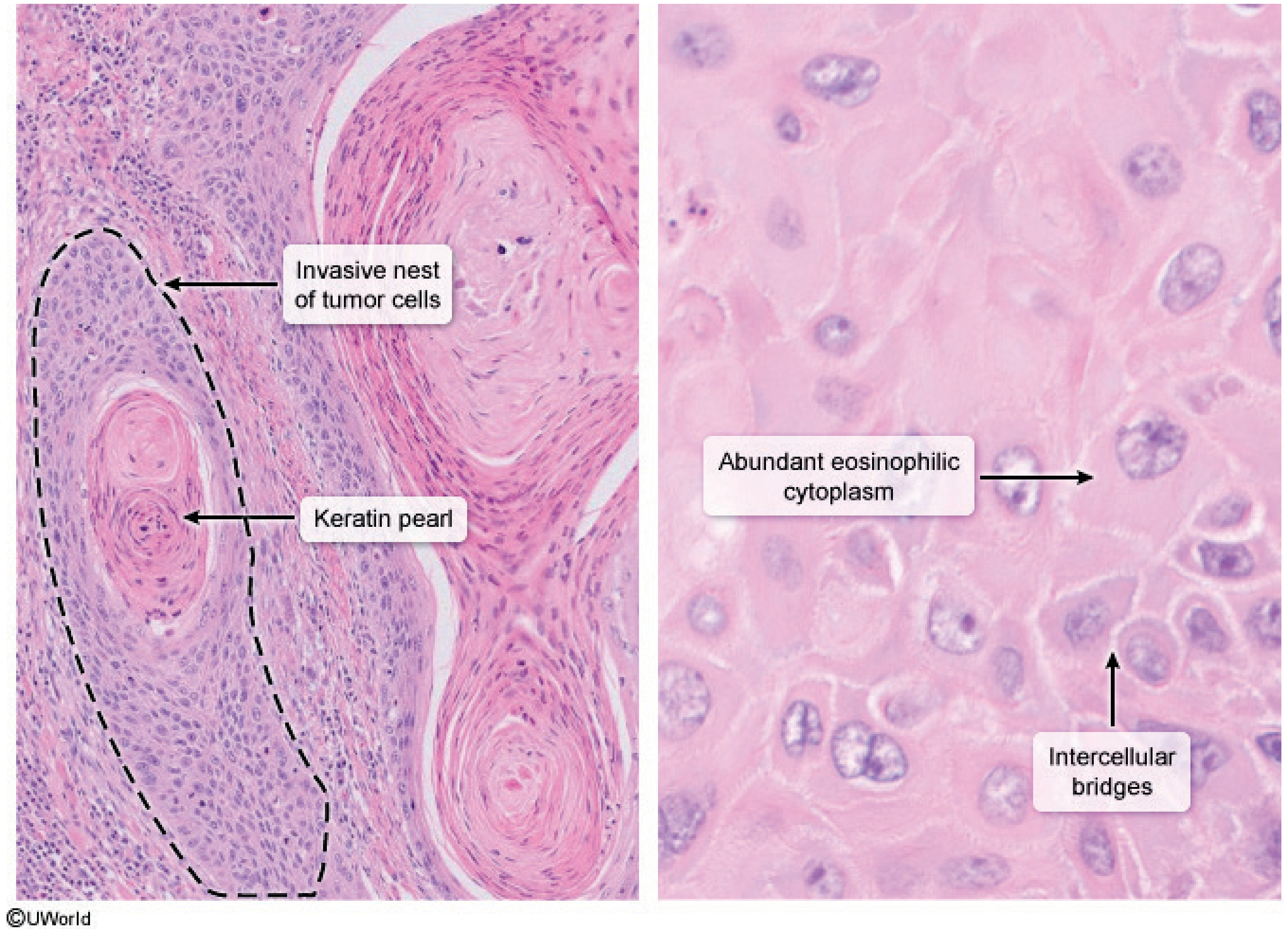
Tumor
origin
spread
lung, li
surrou
not, by

Educa
Tumor
cells' l
involve

Patholog
Subject

Exhibit Display

Well-differentiated squamous cell carcinoma


Invasive nest of tumor cells
Keratin pearl
Abundant eosinophilic cytoplasm
Intercellular bridges

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Copyright © UWorld. All rights reserved.

- Mitotic count
- Distant metastases

Biopsy
Extens
invasi

Furthe
neopla
aggre
norma
grade
the mi
keratir
of mitc

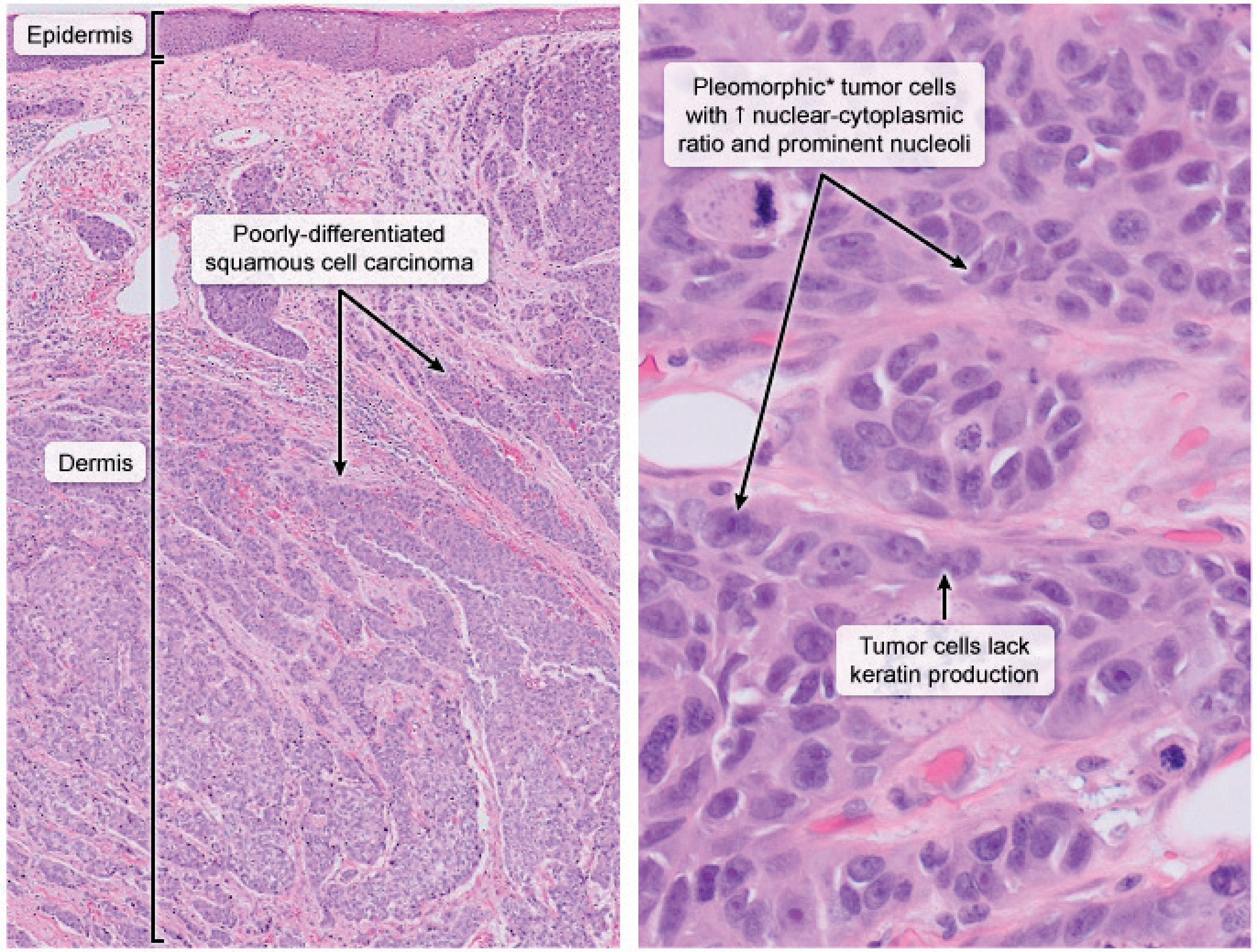
Tumo
origin
spread
lung, li
surrou
not, by

Educa
Tumor
cells' l
involve

Patholo
Subject

Exhibit Display

Poorly-differentiated squamous cell carcinoma

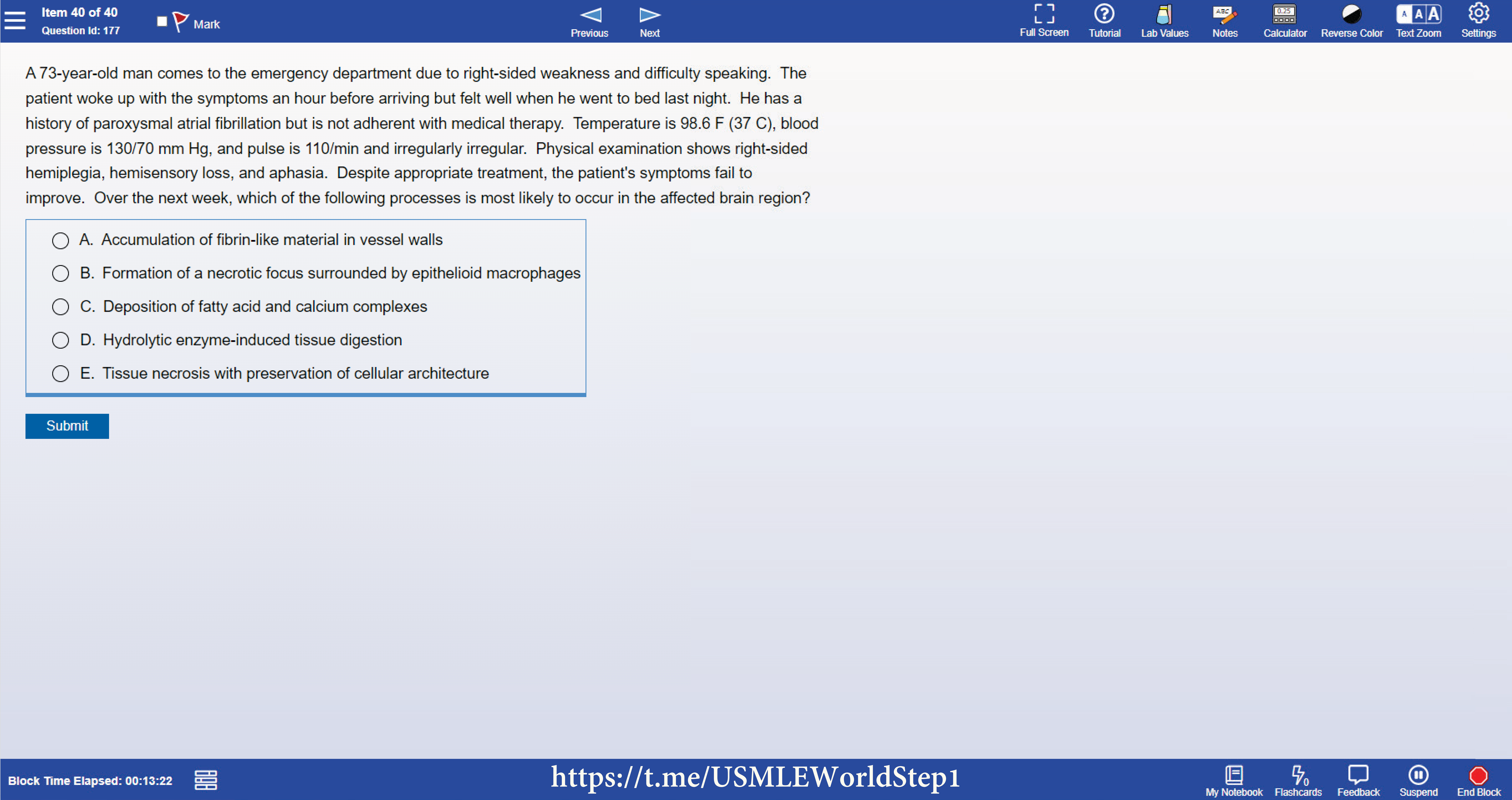

Epidermis
Poorly-differentiated squamous cell carcinoma
Dermis
Pleomorphic* tumor cells with ↑ nuclear-cytoplasmic ratio and prominent nucleoli
Tumor cells lack keratin production

*Variable size and shape.

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Copyright © UWorld. All rights reserved.



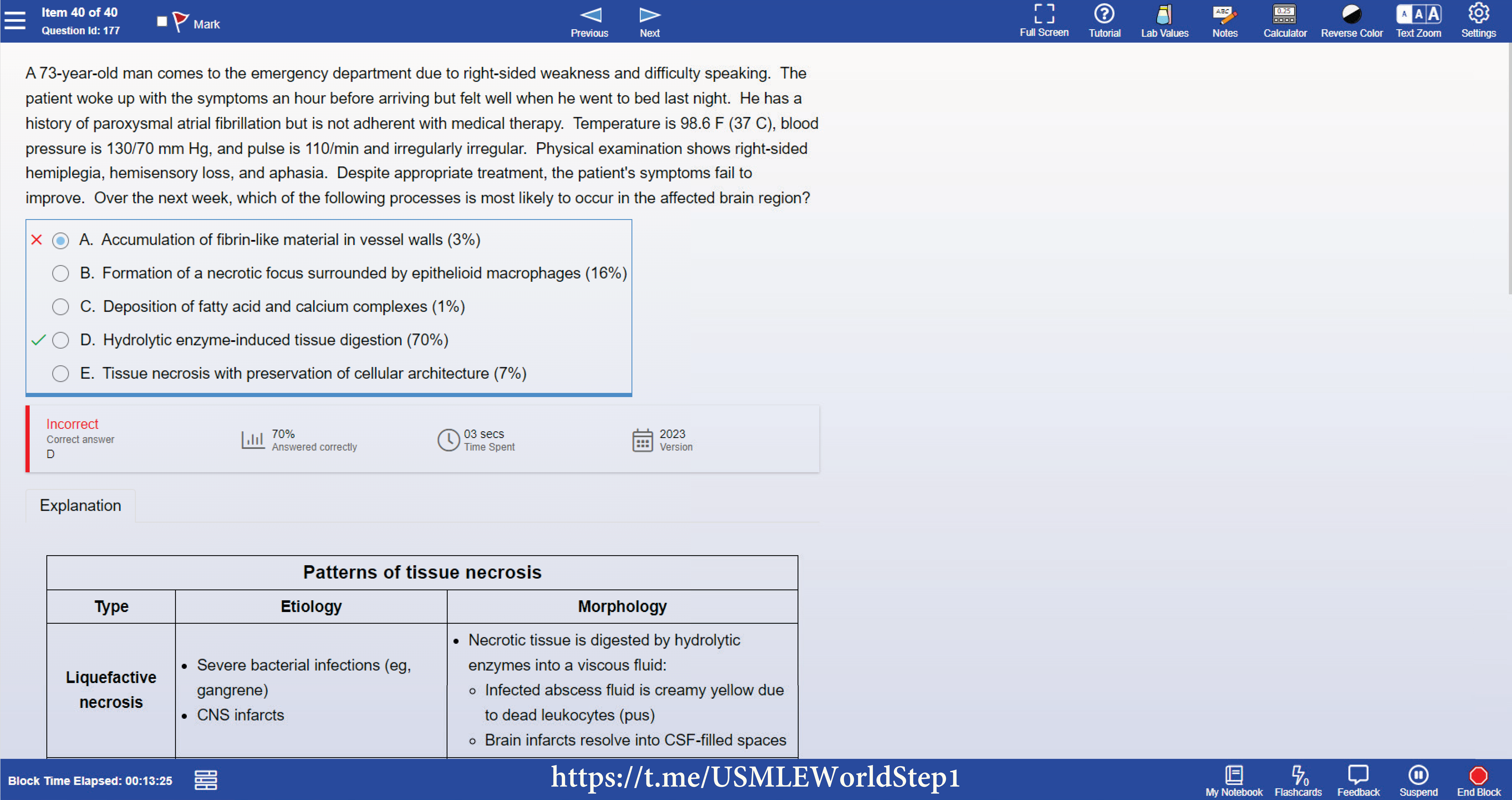
Item 40 of 40
Question Id: 177
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 73-year-old man comes to the emergency department due to right-sided weakness and difficulty speaking. The patient woke up with the symptoms an hour before arriving but felt well when he went to bed last night. He has a history of paroxysmal atrial fibrillation but is not adherent with medical therapy. Temperature is 98.6 F (37 C), blood pressure is 130/70 mm Hg, and pulse is 110/min and irregularly irregular. Physical examination shows right-sided hemiplegia, hemisensory loss, and aphasia. Despite appropriate treatment, the patient's symptoms fail to improve. Over the next week, which of the following processes is most likely to occur in the affected brain region?

- ○ A. Accumulation of fibrin-like material in vessel walls
- ○ B. Formation of a necrotic focus surrounded by epithelioid macrophages
- ○ C. Deposition of fatty acid and calcium complexes
- ○ D. Hydrolytic enzyme-induced tissue digestion
- ○ E. Tissue necrosis with preservation of cellular architecture

Submit
Block Time Elapsed: 00:13:22

My Notebook
Flashcards
Feedback
Suspend
End Block


Item 40 of 40
Question Id: 177
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 73-year-old man comes to the emergency department due to right-sided weakness and difficulty speaking. The patient woke up with the symptoms an hour before arriving but felt well when he went to bed last night. He has a history of paroxysmal atrial fibrillation but is not adherent with medical therapy. Temperature is 98.6 F (37 C), blood pressure is 130/70 mm Hg, and pulse is 110/min and irregularly irregular. Physical examination shows right-sided hemiplegia, hemisensory loss, and aphasia. Despite appropriate treatment, the patient's symptoms fail to improve. Over the next week, which of the following processes is most likely to occur in the affected brain region?

- ✗ ● A. Accumulation of fibrin-like material in vessel walls (3%)
- ○ B. Formation of a necrotic focus surrounded by epithelioid macrophages (16%)
- ○ C. Deposition of fatty acid and calcium complexes (1%)
- ✓ ○ D. Hydrolytic enzyme-induced tissue digestion (70%)
- ○ E. Tissue necrosis with preservation of cellular architecture (7%)

Incorrect
Correct answer
D

70%
Answered correctly

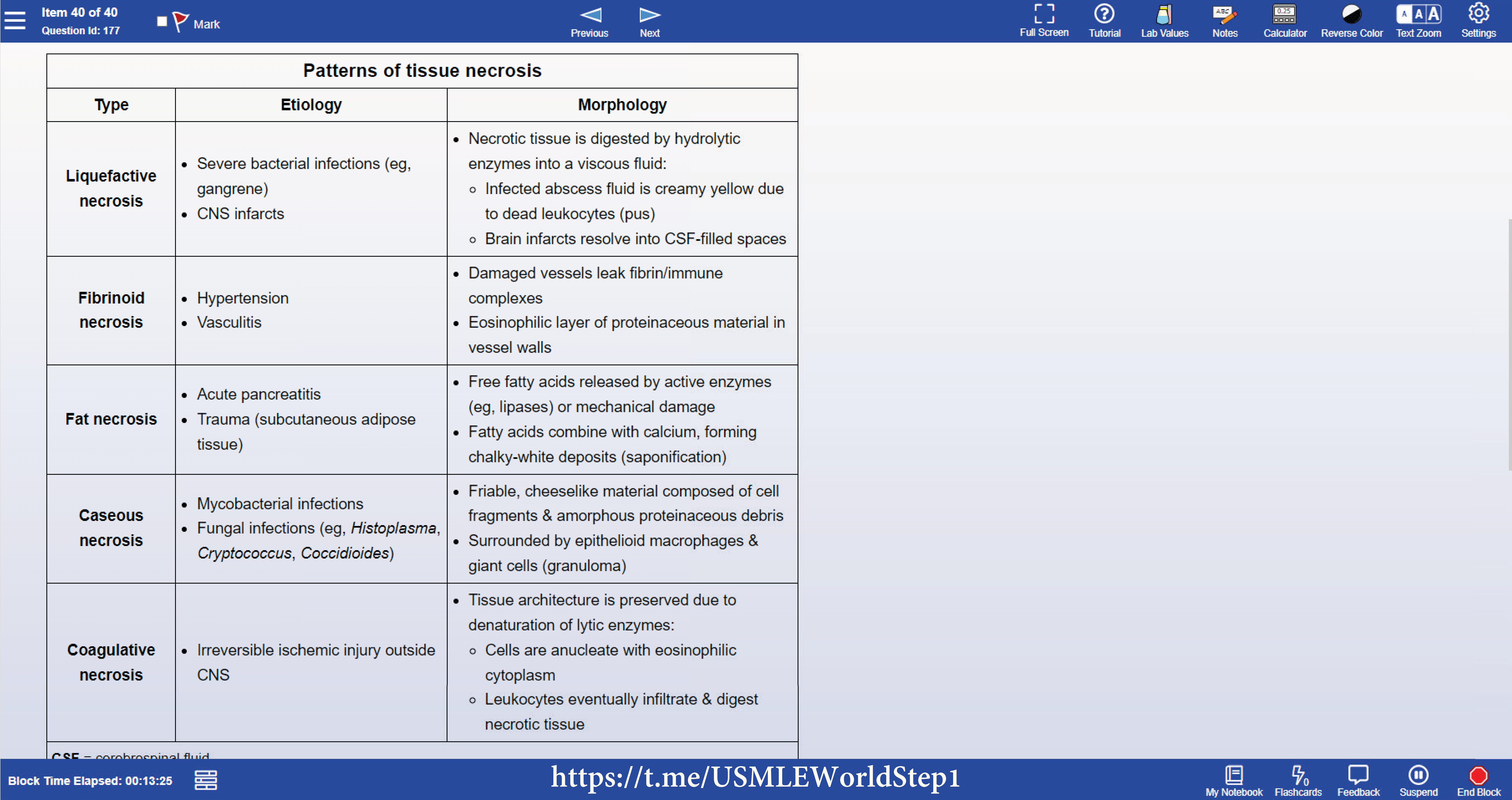
03 secs
Time Spent

2023
Version

Explanation

Patterns of tissue necrosis		
Type	**Etiology**	**Morphology**
Liquefactive necrosis	• Severe bacterial infections (eg, gangrene) • CNS infarcts	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ◦ Infected abscess fluid is creamy yellow due to dead leukocytes (pus) ◦ Brain infarcts resolve into CSF-filled spaces

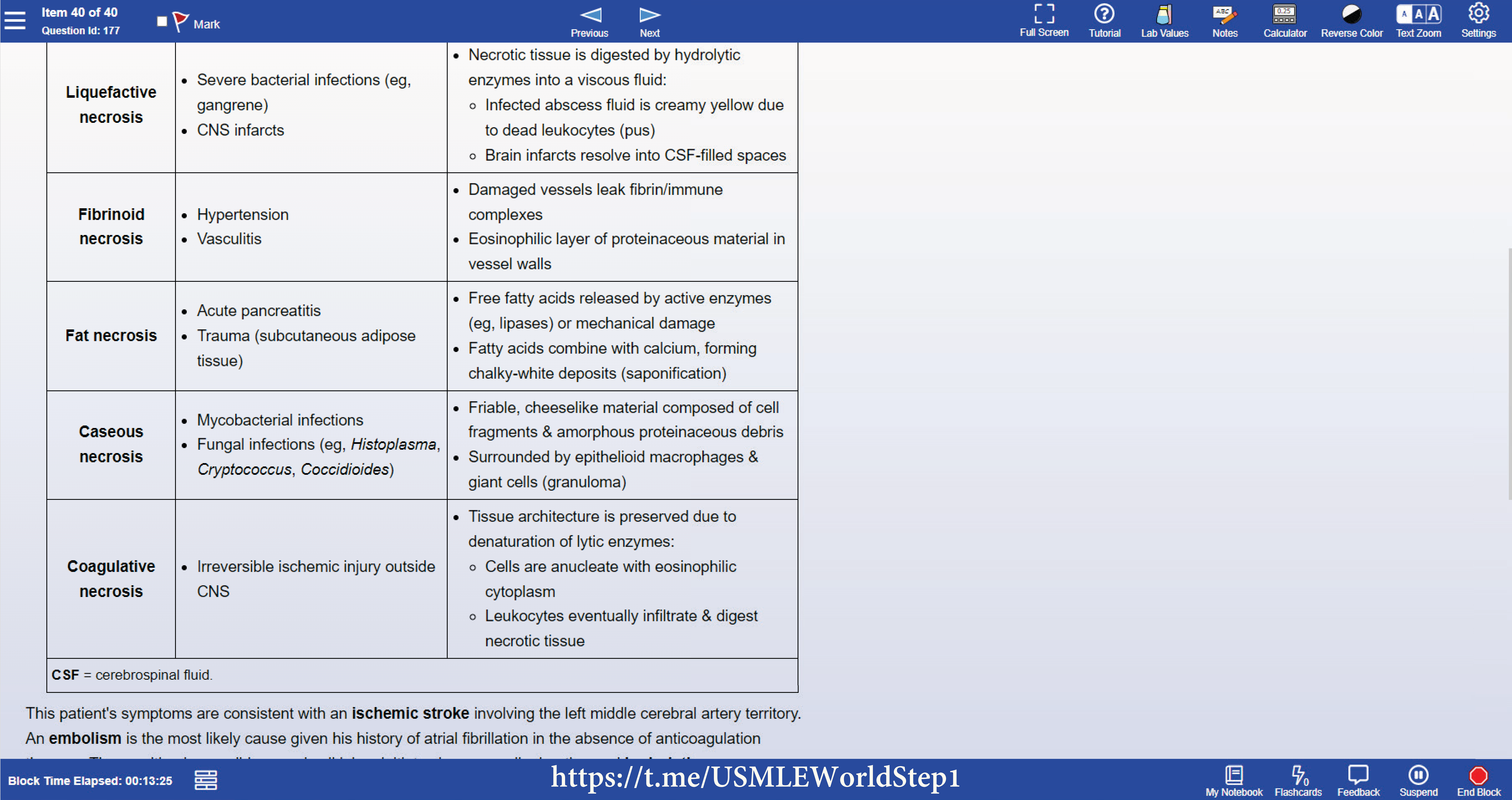
Block Time Elapsed: 00:13:25
My Notebook
Flashcards
Feedback
Suspend
End Block


Item 40 of 40
Question Id: 177
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:13:25
My Notebook
Flashcards
Feedback
Suspend
End Block

Patterns of tissue necrosis

Type	Etiology	Morphology
Liquefactive necrosis	• Severe bacterial infections (eg, gangrene) • CNS infarcts	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ○ Infected abscess fluid is creamy yellow due to dead leukocytes (pus) ○ Brain infarcts resolve into CSF-filled spaces
Fibrinoid necrosis	• Hypertension • Vasculitis	• Damaged vessels leak fibrin/immune complexes • Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	• Acute pancreatitis • Trauma (subcutaneous adipose tissue)	• Free fatty acids released by active enzymes (eg, lipases) or mechanical damage • Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	• Mycobacterial infections • Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	• Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris • Surrounded by epithelioid macrophages & giant cells (granuloma)
Coagulative necrosis	• Irreversible ischemic injury outside CNS	• Tissue architecture is preserved due to denaturation of lytic enzymes: ○ Cells are anucleate with eosinophilic cytoplasm ○ Leukocytes eventually infiltrate & digest necrotic tissue

CSF = cerebrospinal fluid


Item 40 of 40
Question Id: 177
Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
Block Time Elapsed: 00:13:25
My Notebook
Flashcards
Feedback
Suspend
End Block

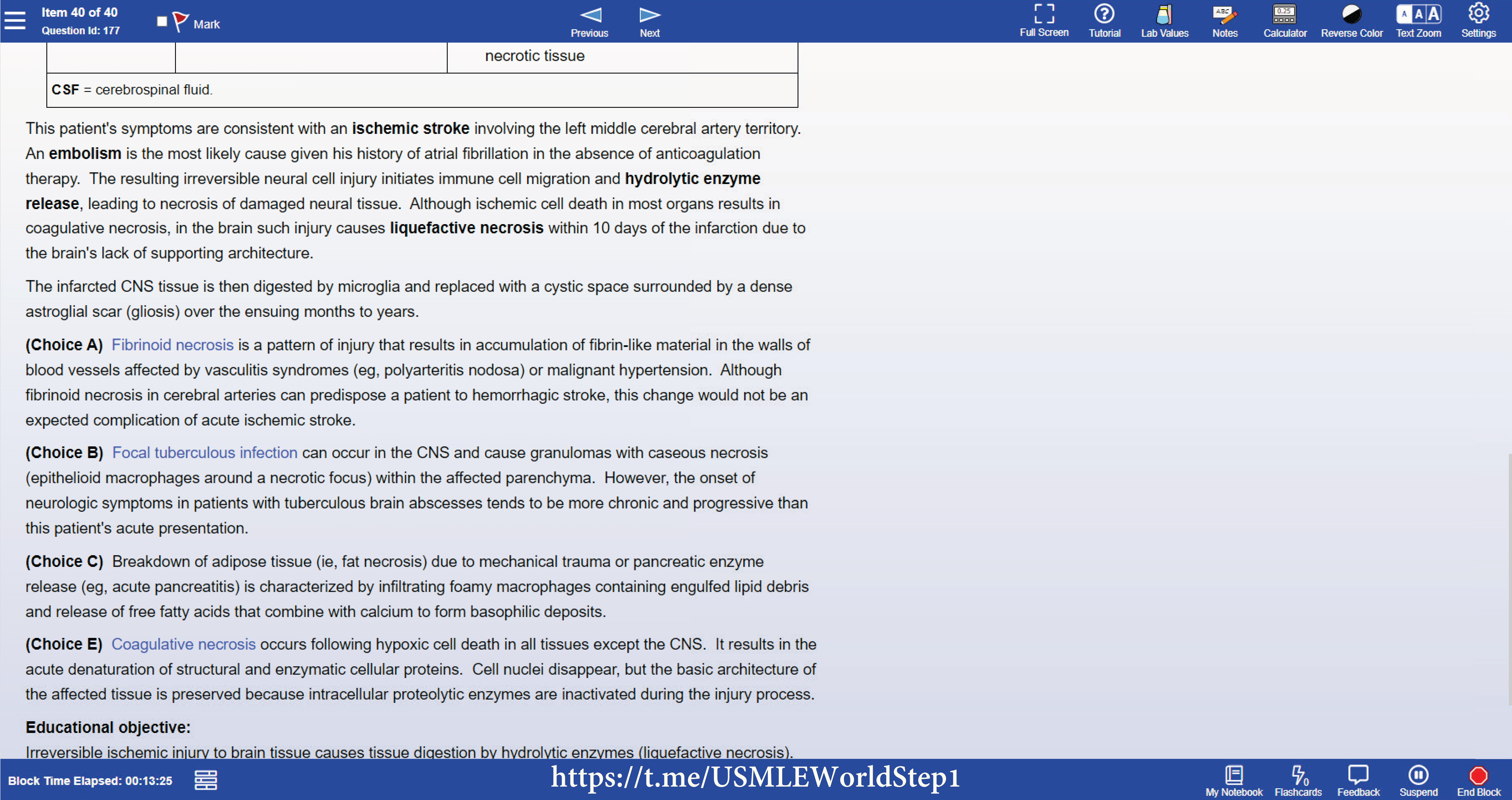
Liquefactive necrosis	- Severe bacterial infections (eg, gangrene)
	- CNS infarcts
		- Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid:
		  - Infected abscess fluid is creamy yellow due to dead leukocytes (pus)
		  - Brain infarcts resolve into CSF-filled spaces

Fibrinoid necrosis	- Hypertension - Vasculitis	- Damaged vessels leak fibrin/immune complexes - Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	- Acute pancreatitis - Trauma (subcutaneous adipose tissue)	- Free fatty acids released by active enzymes (eg, lipases) or mechanical damage - Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	- Mycobacterial infections - Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	- Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris - Surrounded by epithelioid macrophages & giant cells (granuloma)

Coagulative necrosis	- Irreversible ischemic injury outside CNS	- Tissue architecture is preserved due to denaturation of lytic enzymes:
		  - Cells are anucleate with eosinophilic cytoplasm
		  - Leukocytes eventually infiltrate & digest necrotic tissue

CSF = cerebrospinal fluid.

This patient's symptoms are consistent with an **ischemic stroke** involving the left middle cerebral artery territory. An **embolism** is the most likely cause given his history of atrial fibrillation in the absence of anticoagulation



		necrotic tissue
CSF = cerebrospinal fluid.		

This patient's symptoms are consistent with an **ischemic stroke** involving the left middle cerebral artery territory. An **embolism** is the most likely cause given his history of atrial fibrillation in the absence of anticoagulation therapy. The resulting irreversible neural cell injury initiates immune cell migration and **hydrolytic enzyme release**, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to the brain's lack of supporting architecture.

The infarcted CNS tissue is then digested by microglia and replaced with a cystic space surrounded by a dense astroglial scar (gliosis) over the ensuing months to years.

(Choice A) Fibrinoid necrosis is a pattern of injury that results in accumulation of fibrin-like material in the walls of blood vessels affected by vasculitis syndromes (eg, polyarteritis nodosa) or malignant hypertension. Although fibrinoid necrosis in cerebral arteries can predispose a patient to hemorrhagic stroke, this change would not be an expected complication of acute ischemic stroke.

(Choice B) Focal tuberculous infection can occur in the CNS and cause granulomas with caseous necrosis (epithelioid macrophages around a necrotic focus) within the affected parenchyma. However, the onset of neurologic symptoms in patients with tuberculous brain abscesses tends to be more chronic and progressive than this patient's acute presentation.

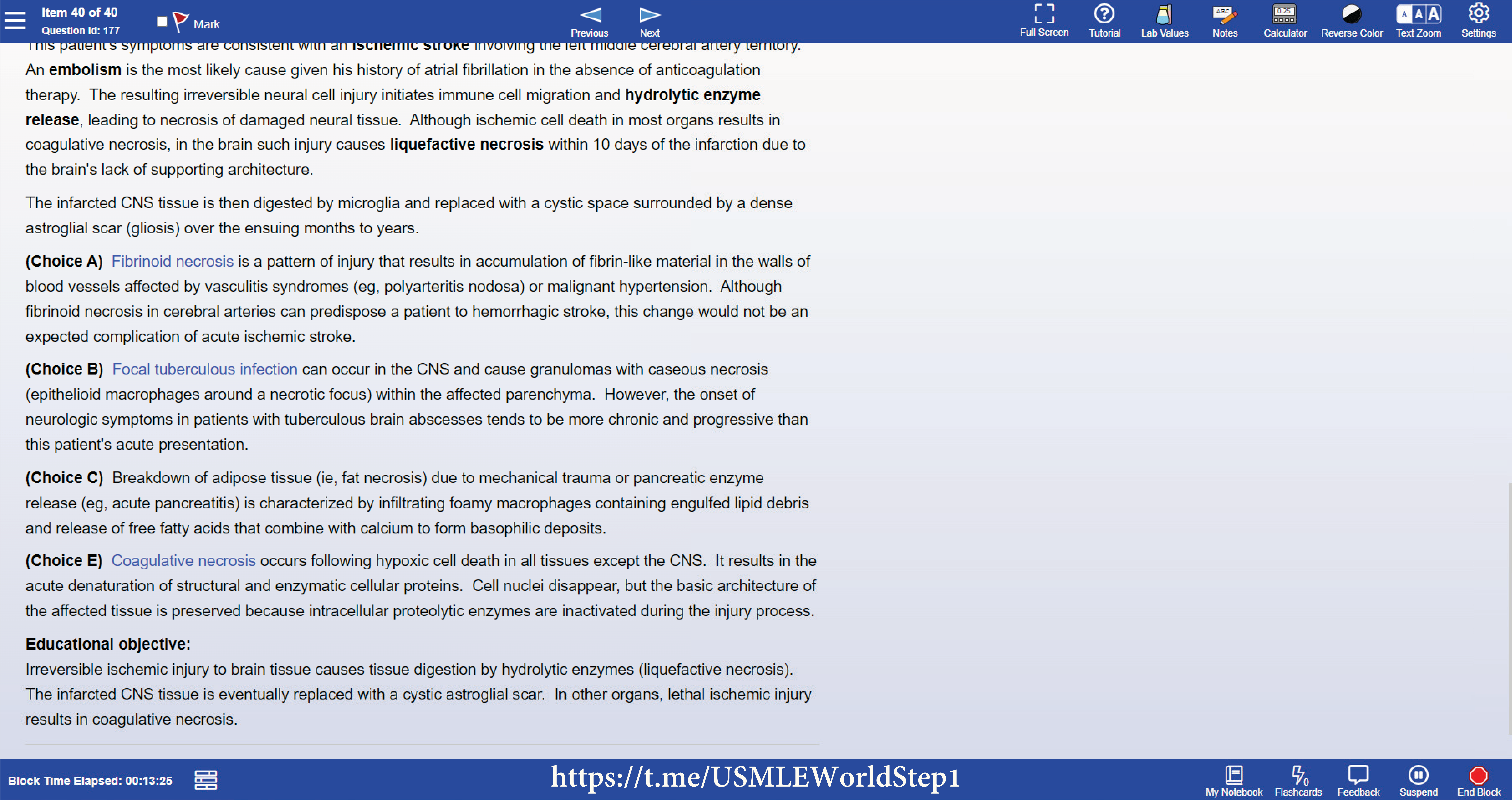
(Choice C) Breakdown of adipose tissue (ie, fat necrosis) due to mechanical trauma or pancreatic enzyme release (eg, acute pancreatitis) is characterized by infiltrating foamy macrophages containing engulfed lipid debris and release of free fatty acids that combine with calcium to form basophilic deposits.

(Choice E) Coagulative necrosis occurs following hypoxic cell death in all tissues except the CNS. It results in the acute denaturation of structural and enzymatic cellular proteins. Cell nuclei disappear, but the basic architecture of the affected tissue is preserved because intracellular proteolytic enzymes are inactivated during the injury process.

Educational objective:

Irreversible ischemic injury to brain tissue causes tissue digestion by hydrolytic enzymes (liquefactive necrosis).

Block Time Elapsed: 00:13:25



This patient's symptoms are consistent with an **ischemic stroke** involving the left middle cerebral artery territory. An **embolism** is the most likely cause given his history of atrial fibrillation in the absence of anticoagulation therapy. The resulting irreversible neural cell injury initiates immune cell migration and **hydrolytic enzyme release**, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to the brain's lack of supporting architecture.

The infarcted CNS tissue is then digested by microglia and replaced with a cystic space surrounded by a dense astroglial scar (gliosis) over the ensuing months to years.

(Choice A) Fibrinoid necrosis is a pattern of injury that results in accumulation of fibrin-like material in the walls of blood vessels affected by vasculitis syndromes (eg, polyarteritis nodosa) or malignant hypertension. Although fibrinoid necrosis in cerebral arteries can predispose a patient to hemorrhagic stroke, this change would not be an expected complication of acute ischemic stroke.

(Choice B) Focal tuberculous infection can occur in the CNS and cause granulomas with caseous necrosis (epithelioid macrophages around a necrotic focus) within the affected parenchyma. However, the onset of neurologic symptoms in patients with tuberculous brain abscesses tends to be more chronic and progressive than this patient's acute presentation.

(Choice C) Breakdown of adipose tissue (ie, fat necrosis) due to mechanical trauma or pancreatic enzyme release (eg, acute pancreatitis) is characterized by infiltrating foamy macrophages containing engulfed lipid debris and release of free fatty acids that combine with calcium to form basophilic deposits.

(Choice E) Coagulative necrosis occurs following hypoxic cell death in all tissues except the CNS. It results in the acute denaturation of structural and enzymatic cellular proteins. Cell nuclei disappear, but the basic architecture of the affected tissue is preserved because intracellular proteolytic enzymes are inactivated during the injury process.

Educational objective:
Irreversible ischemic injury to brain tissue causes tissue digestion by hydrolytic enzymes (liquefactive necrosis). The infarcted CNS tissue is eventually replaced with a cystic astroglial scar. In other organs, lethal ischemic injury results in coagulative necrosis.

release, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to the bra

The in
astrog

(Choi
blood
fibrino
expect

(Choi
(epithe
neurol
this pa

(Choi
releas
and re

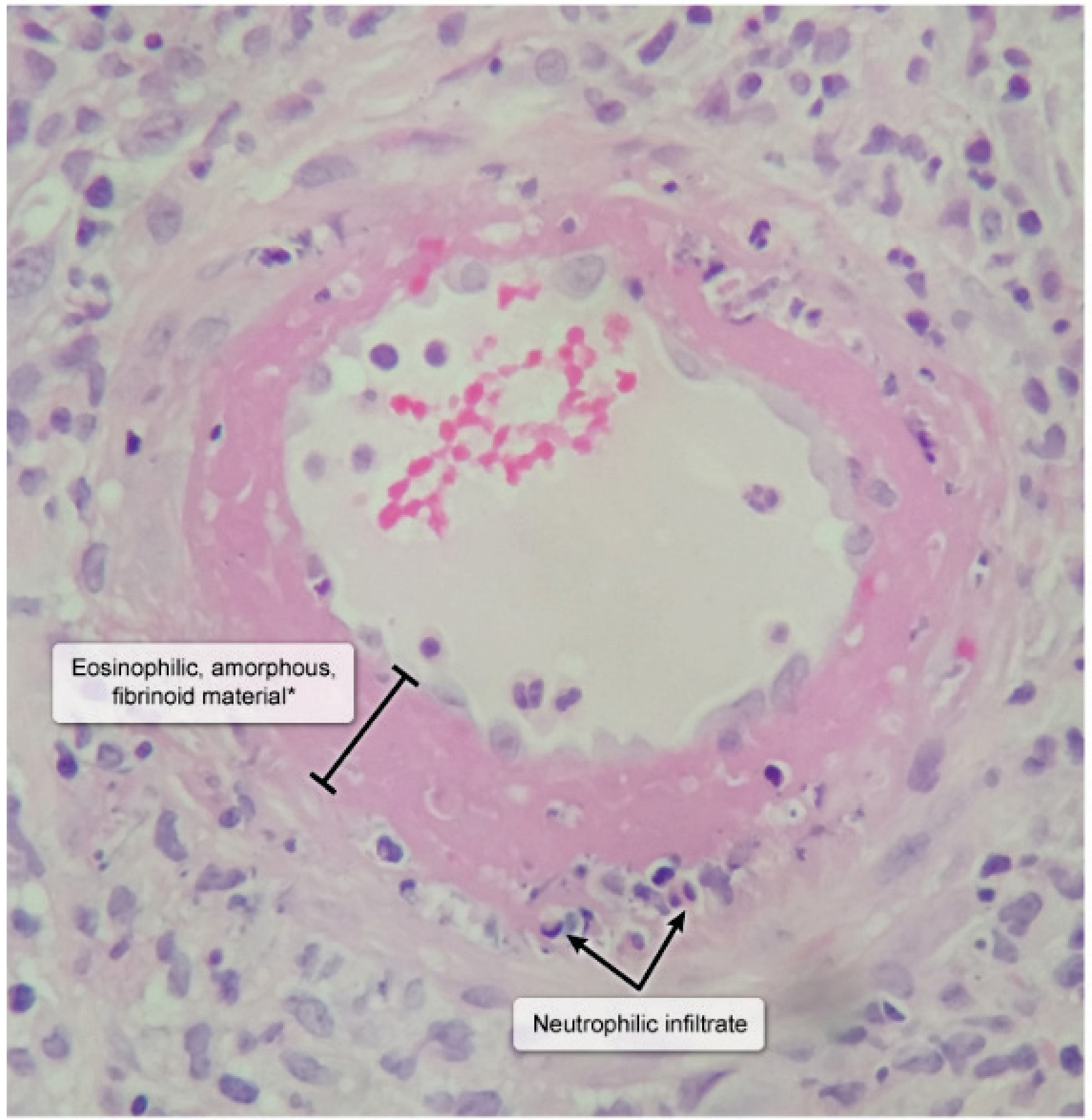
(Choi
acute
the aff

Educa
Irrever
The in
results

Patholo
Subject

Exhibit Display

Fibrinoid necrosis


Eosinophilic, amorphous, fibrinoid material*
Neutrophilic infiltrate

*Deposits of immune complexes with fibrin in vessel wall

©UWorld

Zoom In Zoom Out Reset New | Existing My Notebook

Copyright © UWorld. All rights reserved.

release, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to the bra

The in
astrog

(Choi
blood
fibrino
expect

(Choi
(epithe
neurol
this pa

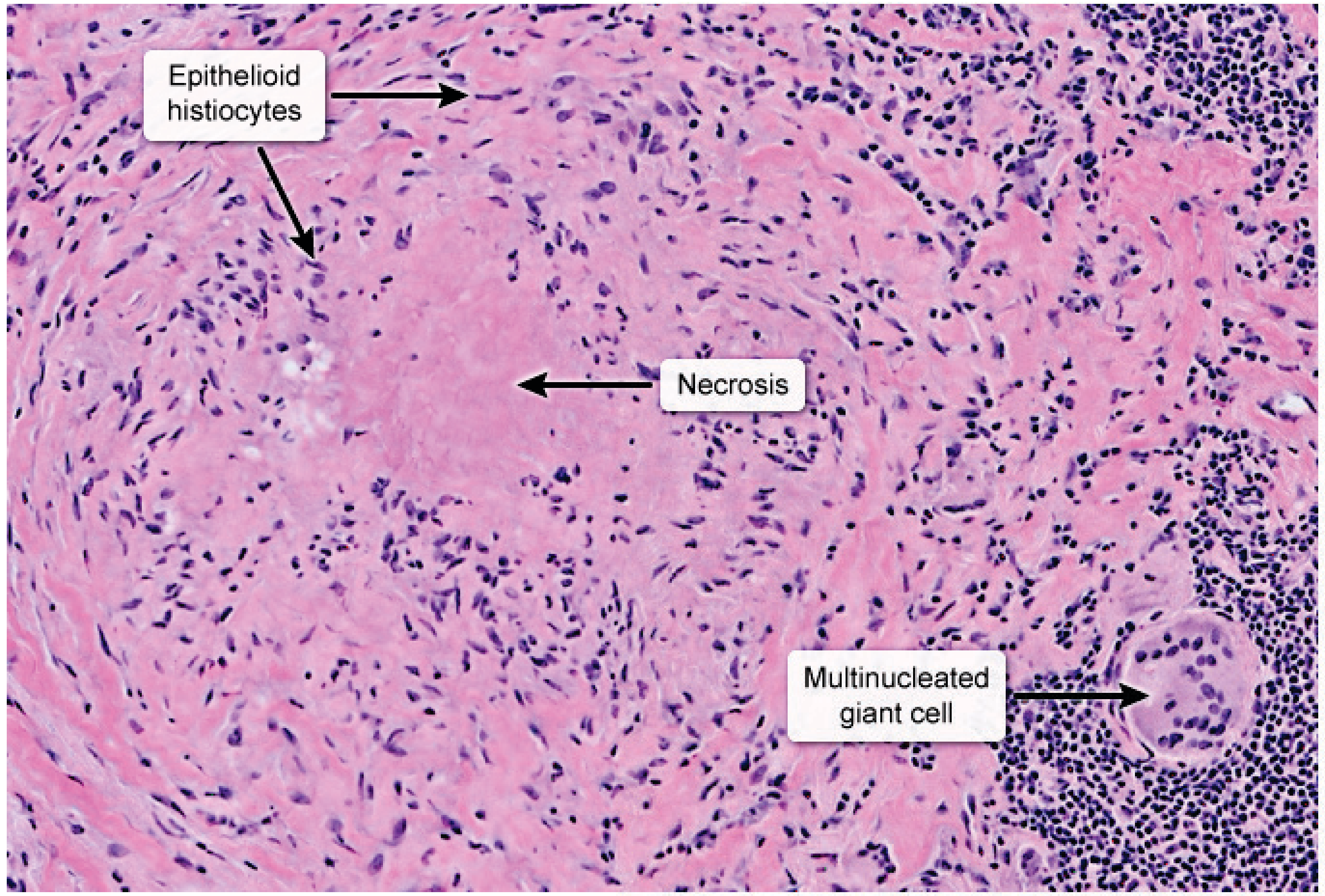
(Choi
releas
and re

(Choi
acute
the aff

Educa
Irrever
The in
results

Exhibit Display

Caseating granuloma

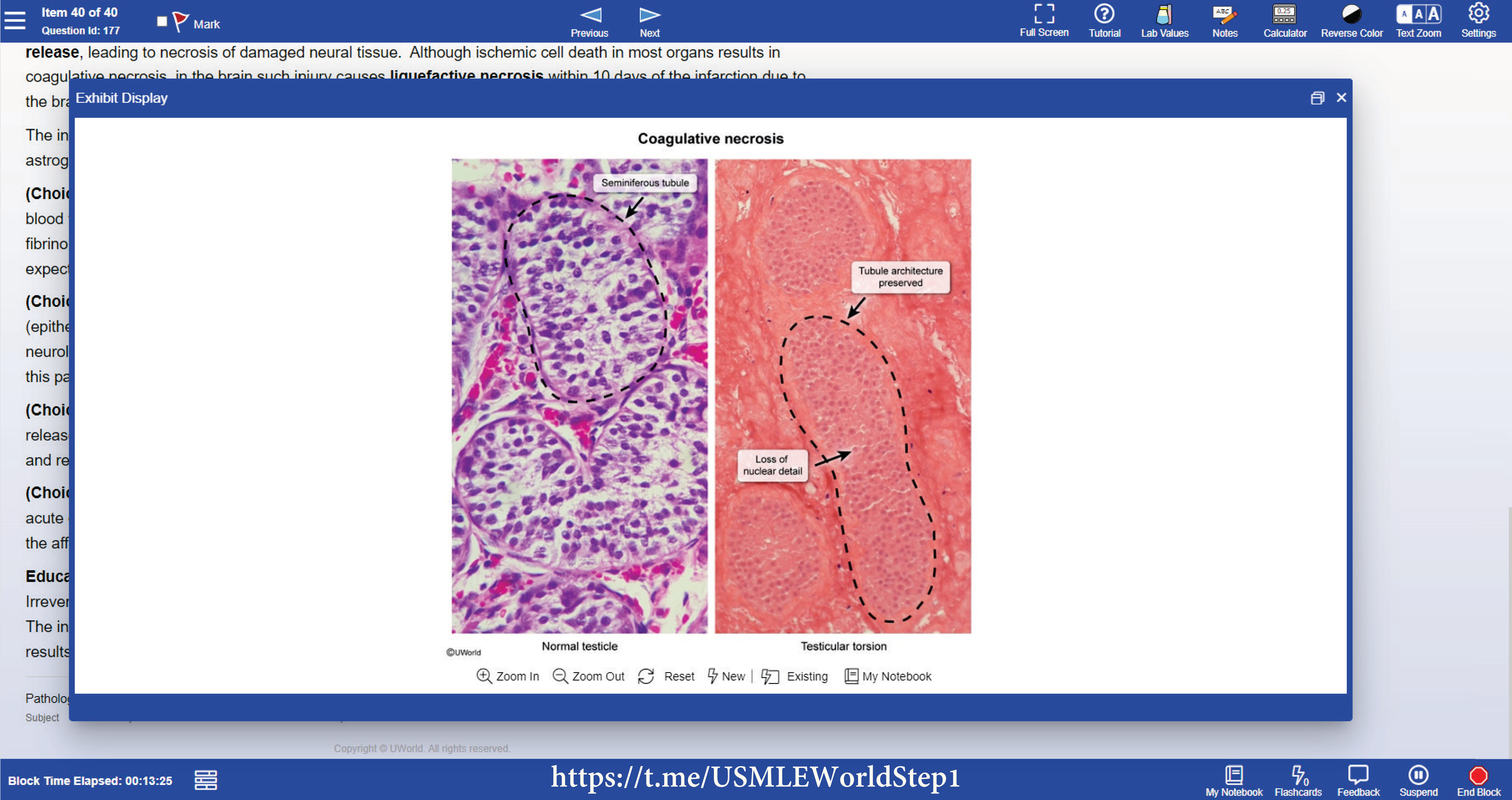

Epithelioid histiocytes
Necrosis
Multinucleated giant cell

©UWorld

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Pathology	Pathology (General Principles)	Necrosis
Subject	System	Topic

Copyright © UWorld. All rights reserved.


Item 40 of 40
Question Id: 177
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

release, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to

the bra

The in
astrog

(Choi
blood
fibrino
expect

(Choi
(epithe
neurol
this pa

(Choi
releas
and re

(Choi
acute
the aff

Educa
Irrever
The in
results

Patholo
Subject

Exhibit Display

Coagulative necrosis

Seminiferous tubule
Tubule architecture preserved
Loss of nuclear detail
©UWorld

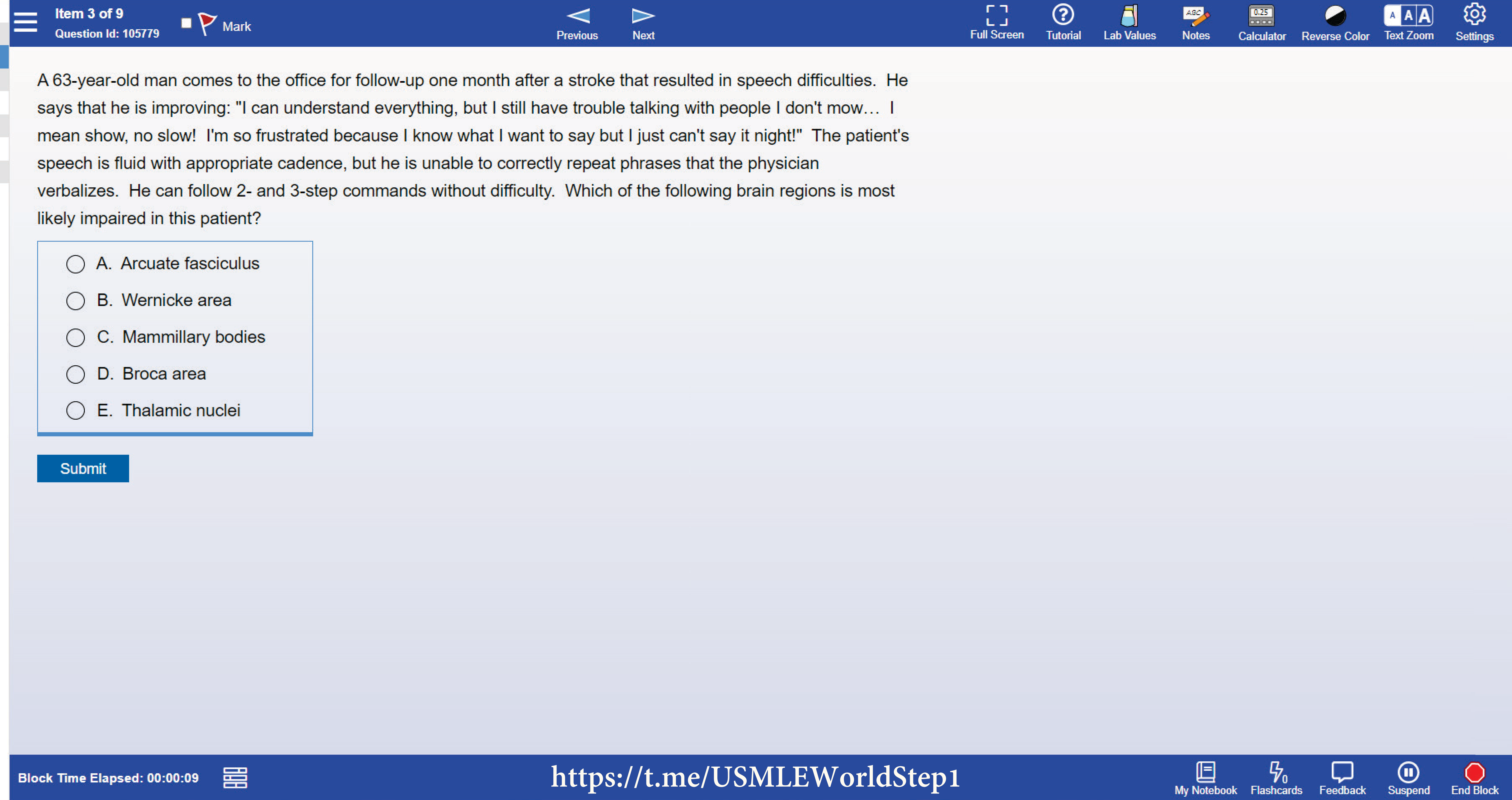
Normal testicle

Testicular torsion

Zoom In
Zoom Out
Reset
New
Existing
My Notebook

Copyright © UWorld. All rights reserved.

Block Time Elapsed: 00:13:25
My Notebook
Flashcards
Feedback
Suspend
End Block


Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings
My Notebook
Flashcards
Feedback
Suspend
End Block

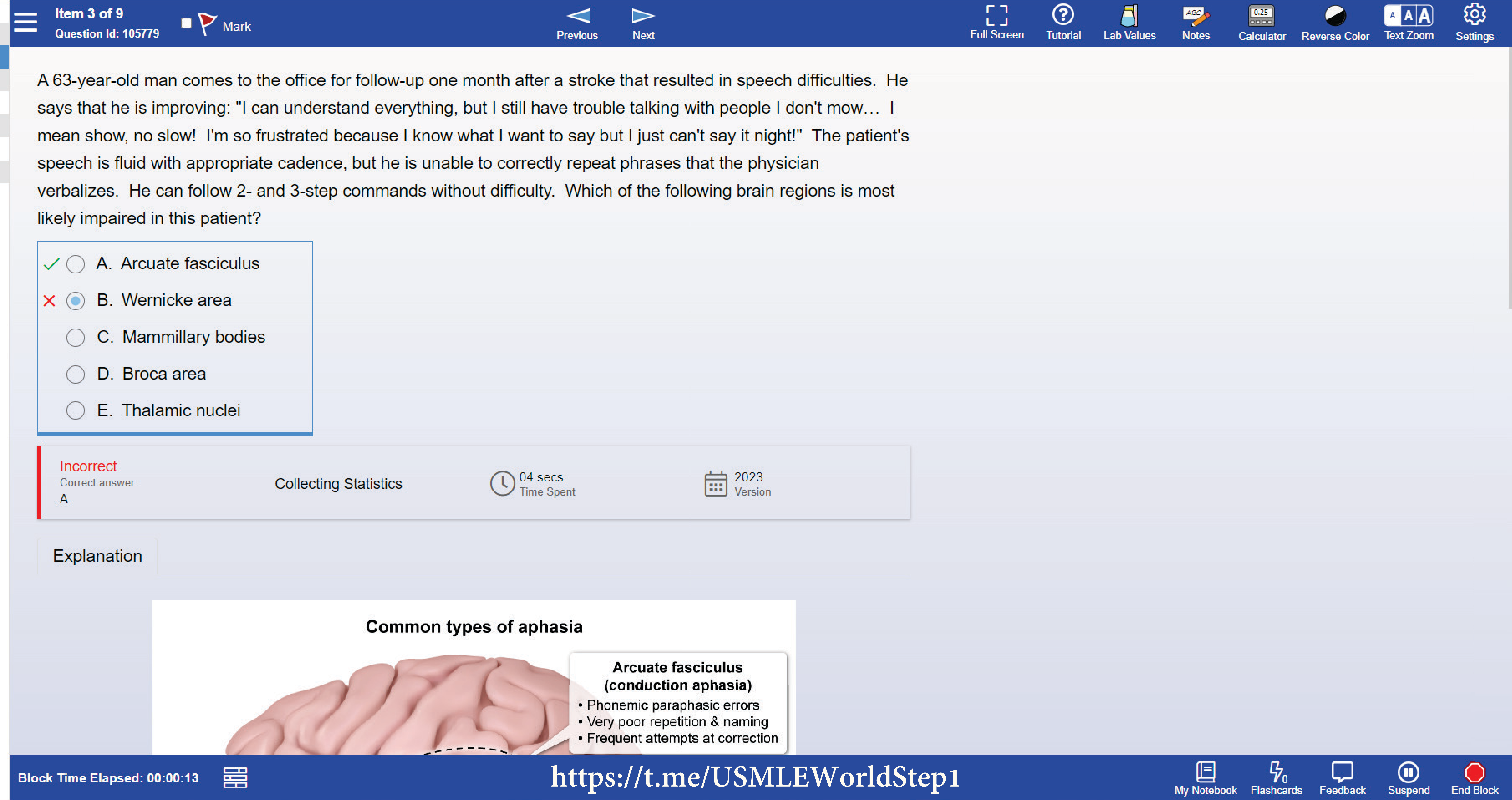
Item 3 of 9
Question Id: 105779

A 63-year-old man comes to the office for follow-up one month after a stroke that resulted in speech difficulties. He says that he is improving: "I can understand everything, but I still have trouble talking with people I don't mow… I mean show, no slow! I'm so frustrated because I know what I want to say but I just can't say it night!" The patient's speech is fluid with appropriate cadence, but he is unable to correctly repeat phrases that the physician verbalizes. He can follow 2- and 3-step commands without difficulty. Which of the following brain regions is most likely impaired in this patient?

○ A. Arcuate fasciculus
○ B. Wernicke area
○ C. Mammillary bodies
○ D. Broca area
○ E. Thalamic nuclei

Submit

Block Time Elapsed: 00:00:09


Item 3 of 9
Question Id: 105779
☐ Mark
Previous
Next
Full Screen
Tutorial
Lab Values
Notes
Calculator
Reverse Color
Text Zoom
Settings

A 63-year-old man comes to the office for follow-up one month after a stroke that resulted in speech difficulties. He says that he is improving: "I can understand everything, but I still have trouble talking with people I don't mow… I mean show, no slow! I'm so frustrated because I know what I want to say but I just can't say it night!" The patient's speech is fluid with appropriate cadence, but he is unable to correctly repeat phrases that the physician verbalizes. He can follow 2- and 3-step commands without difficulty. Which of the following brain regions is most likely impaired in this patient?

✓ ○ A. Arcuate fasciculus

✗ ● B. Wernicke area

○ C. Mammillary bodies

○ D. Broca area

○ E. Thalamic nuclei

Incorrect
Correct answer
A

Collecting Statistics

04 secs
Time Spent

2023
Version

Explanation

Common types of aphasia

Arcuate fasciculus
(conduction aphasia)
- Phonemic paraphasic errors
- Very poor repetition & naming
- Frequent attempts at correction

Block Time Elapsed: 00:00:13

My Notebook
Flashcards
Feedback
Suspend
End Block

Incorrect
Correct answer
A

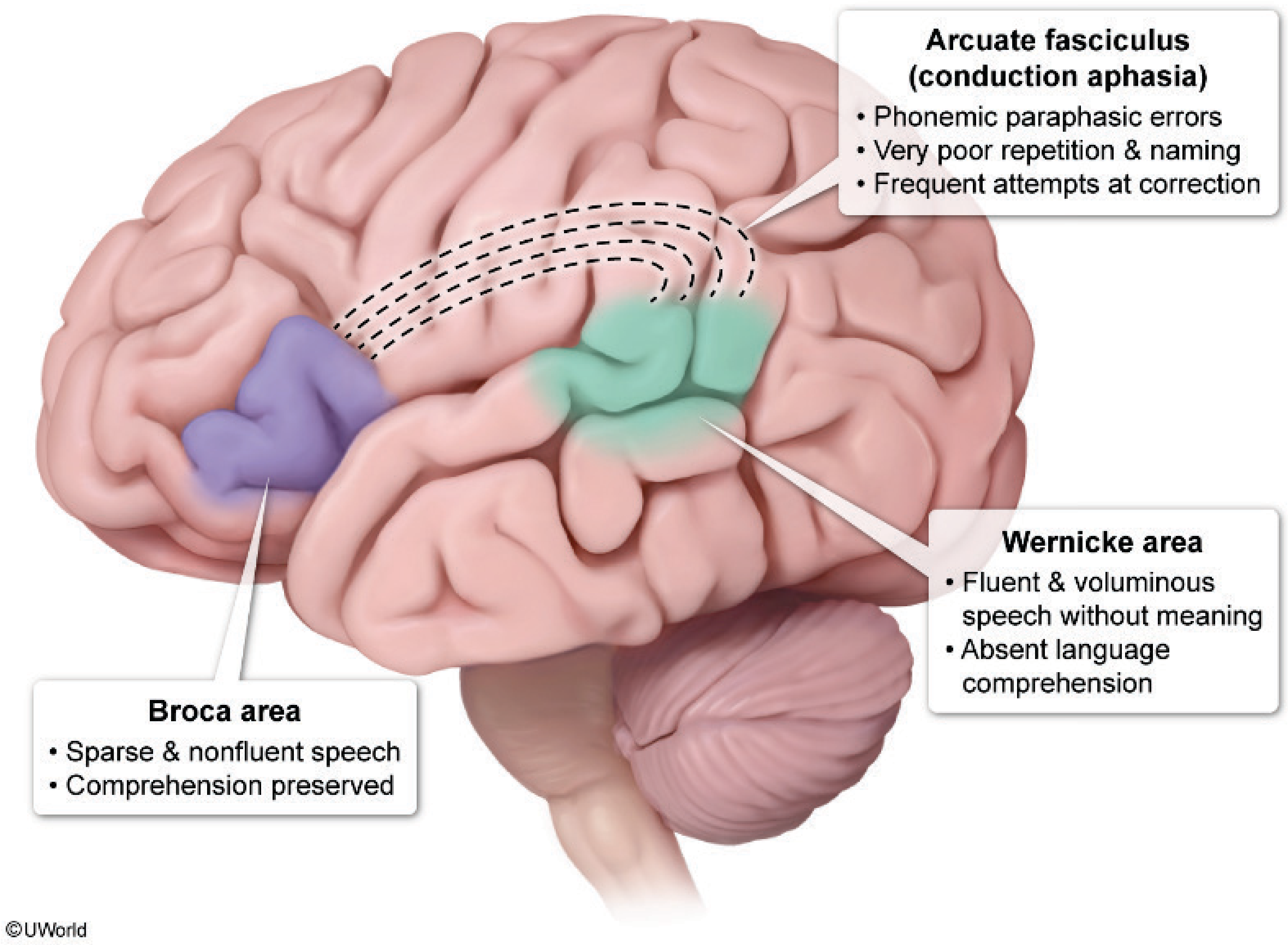
Collecting Statistics

04 secs
Time Spent

2023
Version

Exhibit Display

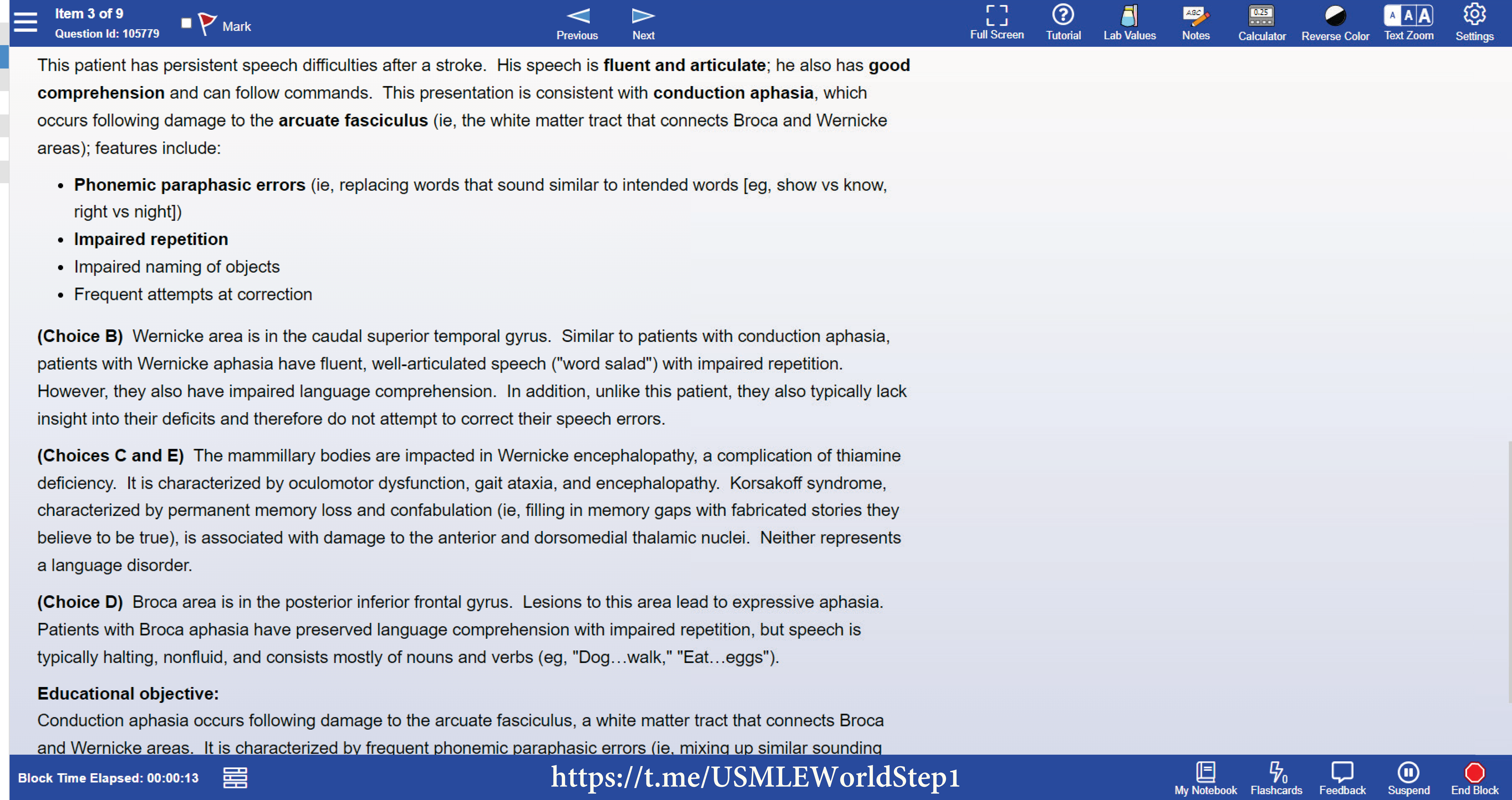
Common types of aphasia


Arcuate fasciculus (conduction aphasia)
• Phonemic paraphasic errors
• Very poor repetition & naming
• Frequent attempts at correction
Wernicke area
• Fluent & voluminous speech without meaning
• Absent language comprehension
Broca area
• Sparse & nonfluent speech
• Comprehension preserved
©UWorld

Zoom In | Zoom Out | Reset | New | Existing | My Notebook

This

comprehension and can follow commands. This presentation is consistent with **conduction aphasia**, which



This patient has persistent speech difficulties after a stroke. His speech is **fluent and articulate**; he also has **good comprehension** and can follow commands. This presentation is consistent with **conduction aphasia**, which occurs following damage to the **arcuate fasciculus** (ie, the white matter tract that connects Broca and Wernicke areas); features include:

- **Phonemic paraphasic errors** (ie, replacing words that sound similar to intended words [eg, show vs know, right vs night])
- **Impaired repetition**
- Impaired naming of objects
- Frequent attempts at correction

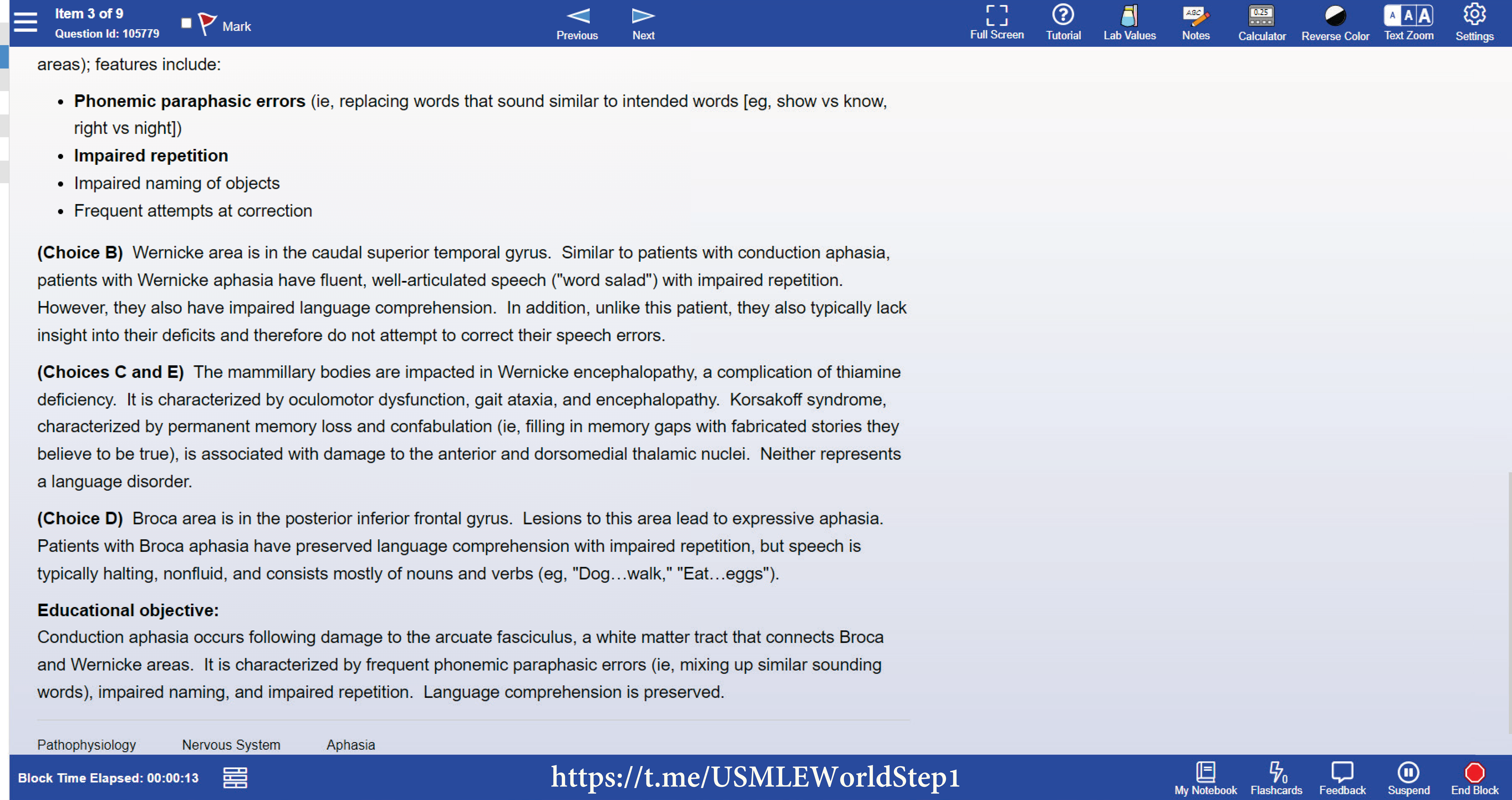
(Choice B) Wernicke area is in the caudal superior temporal gyrus. Similar to patients with conduction aphasia, patients with Wernicke aphasia have fluent, well-articulated speech ("word salad") with impaired repetition. However, they also have impaired language comprehension. In addition, unlike this patient, they also typically lack insight into their deficits and therefore do not attempt to correct their speech errors.

(Choices C and E) The mammillary bodies are impacted in Wernicke encephalopathy, a complication of thiamine deficiency. It is characterized by oculomotor dysfunction, gait ataxia, and encephalopathy. Korsakoff syndrome, characterized by permanent memory loss and confabulation (ie, filling in memory gaps with fabricated stories they believe to be true), is associated with damage to the anterior and dorsomedial thalamic nuclei. Neither represents a language disorder.

(Choice D) Broca area is in the posterior inferior frontal gyrus. Lesions to this area lead to expressive aphasia. Patients with Broca aphasia have preserved language comprehension with impaired repetition, but speech is typically halting, nonfluid, and consists mostly of nouns and verbs (eg, "Dog…walk," "Eat…eggs").

Educational objective:

Conduction aphasia occurs following damage to the arcuate fasciculus, a white matter tract that connects Broca and Wernicke areas. It is characterized by frequent phonemic paraphasic errors (ie, mixing up similar sounding



areas); features include:

- **Phonemic paraphasic errors** (ie, replacing words that sound similar to intended words [eg, show vs know, right vs night])
- **Impaired repetition**
- Impaired naming of objects
- Frequent attempts at correction

(Choice B) Wernicke area is in the caudal superior temporal gyrus. Similar to patients with conduction aphasia, patients with Wernicke aphasia have fluent, well-articulated speech ("word salad") with impaired repetition. However, they also have impaired language comprehension. In addition, unlike this patient, they also typically lack insight into their deficits and therefore do not attempt to correct their speech errors.

(Choices C and E) The mammillary bodies are impacted in Wernicke encephalopathy, a complication of thiamine deficiency. It is characterized by oculomotor dysfunction, gait ataxia, and encephalopathy. Korsakoff syndrome, characterized by permanent memory loss and confabulation (ie, filling in memory gaps with fabricated stories they believe to be true), is associated with damage to the anterior and dorsomedial thalamic nuclei. Neither represents a language disorder.

(Choice D) Broca area is in the posterior inferior frontal gyrus. Lesions to this area lead to expressive aphasia. Patients with Broca aphasia have preserved language comprehension with impaired repetition, but speech is typically halting, nonfluid, and consists mostly of nouns and verbs (eg, "Dog…walk," "Eat…eggs").

Educational objective:
Conduction aphasia occurs following damage to the arcuate fasciculus, a white matter tract that connects Broca and Wernicke areas. It is characterized by frequent phonemic paraphasic errors (ie, mixing up similar sounding words), impaired naming, and impaired repetition. Language comprehension is preserved.

Pathophysiology Nervous System Aphasia

Block Time Elapsed: 00:00:13